Nouvelle théorie hémodynamique " flux et rythme " : concept et applications précliniques en utilisant des nouveaux dispositifs d'assistance circulatoire directeur

Sayed Nour

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Sayed NOUR

Nouvelle Théorie Hémodynamique

« Flux et Rythme »

Concept et applications précliniques en utilisant des nouveaux dispositifs d'assistance circulatoire

Directeur de thèse : Juan Carlos Chachques Professeur, Directeur Recherche HEGP

Composition du jury :

Président du jury :	Alain CARPENTIER	Professeur des Universités, HEGP
Rapporteurs :	Alain SERRAF	Professeur Hôpital Jacques Cartier
	Olivier JEGADEN	Professeur Université de Lyon
Examinateurs :	Claude PLANCHE	Professeur Université Paris-Sud 11
	J.F. RENAUD de la FAVERIE	Directeur de Recherche INSERM
	Olivier PONZIO	Chargé de Recherche, HEGP

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Le Cœur dans l'Egypte ancienne

O Egypte, Egypte! De tes rites religieux, rien ne survivra que des fables que les enfants de vos enfants ne croiront pas. Aucune trace de ta piété ne survivra que par des mots gravés dans la pierre … Asclépios III. 25, {W. Scott. Hermetica, i.1924 ; p.342}.

Pour **l'Egypte,** mon pays d'origine, dans l'espoir que cela puisse contribuer à une continuité des recherches scientifiques internationales.

Pour ma bien-aimée, **Mère** et les arômes de son inoubliable mémoire une petite reconnaissance pour ses grandes vertus, son apprentissage, ses sacrifices et son encouragement pour aimer la science et de l'apprentissage.

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Professeur Alain Carpentier
Claude Planché
Juan Carlos Chachques
Alain Serraf
Olivier Jegaden
Renaud de la Faverie
Olivier Ponzio
Michel Mazmanien
Wu Guifu
Wang Qinmei
Yves Lecarpentier
Madame Sophie Carpentier
Philippe Menasché
Gong Dai
Daya Yang
Daniel Carbognani
Nermine Lila

Résumé

Nouvelle Théorie Hémodynamique **« Flux et Rythme** » **:** *Concept et applications précliniques utilisant de nouveaux dispositifs d'assistance circulatoire*.

Le cœur et les vaisseaux sanguins sont directement issus de l'endothélium et dépendent de sa fonction. Le cœur ne représente pas la seule force motrice de notre système circulatoire, la plupart des stratégies thérapeutiques actuelles des maladies cardiovasculaires sont encore focalisées sur le cœur, négligeant l'ensemble du système circulatoire et le système endothélial. Par exemple, le développement de Dispositifs d'Assistance Cardiaque (DAC) est influencé par le cœur, conçu pour suivre, obéir et doit être synchronisé avec un organe malade.

De nombreux « signaux » de nature différente sont capables d'activer les cellules endothéliales : les forces de cisaillement créées par le flux sanguin parallèle à la surface de la paroi des vaisseaux, mais également les forces perpendiculaires provoquées par l'étirement de la paroi artérielle par les variations de la pression et la qualité cyclique de ces forces. L'activation de cellules endothéliales est due à la pulsatilité du flux mais aussi à l'action de substances vasoactives et des médiateurs de l'inflammation.

Dans notre travail de thèse, nous proposons une nouvelle approche thérapeutique, basée sur une révision fondamentale de l'ensemble du système circulatoire: exposer les défauts de la gestion courante des maladies cardiovasculaires (MCV). Notre nouveau concept se concentre sur la dynamique des flux sanguins pour stimuler, restaurer et maintenir la fonction endothéliale, et compris le cœur lui-même. Nous avons développé et évalué une nouvelle génération de DAC pulsatiles, testée in vitro et in vivo.

Pendant le déroulement de cette thèse nous avons effectué les études suivantes:

1. Etude d'un prototype de cathéter pulsatile. Il est testé de manière isolée dans un modèle expérimental d'ischémie aiguë du myocarde et dans un modèle d'hypertension pulmonaire aiguë.
2. Etude d'un prototype de tube pulsatile à double lumière. Il est testé in-vitro dans un circuit de circulation extracorporelle, et in vivo comme assistance ventriculaire gauche.

3. Etude d’un prototype de combinaison pulsatile. Il est testé sur un modèle animal présentant une défaillance aiguë du ventricule droit. Des prototypes de masques et de pantalons pulsatiles sont en développement.

En conclusion, notre approche est basée sur l’activation de la fonction endothéliale plutôt qu’en une assistance cardiaque directe. Ce concept permet une meilleure gestion thérapeutique des maladies circulatoires et cardio-pulmonaires.

MOTS-CLES : Défaillance circulatoire et cardio-pulmonaires. Force de cisaillement. Fonction endothéliale. Assistance circulatoire pulsatile.

Summary

New Hemodynamic Theory "**Flow and Rate**": *Concept and clinical applications using new pulsatile circulatory assist devices*.

The "Heart" is still considered as the main organ to be dealt with, in case of cardiovascular disease. Nevertheless, the heart is not the only driving force in our circulatory system. In fact, the heart and blood vessels are the direct issues of the endothelium and depend on its function. Moreover, almost all current therapeutic strategies are still focusing on the heart and neglecting the entire circulatory-endothelial system. For example, development of cardiac assist devices (CAD) is still restrained by the heart, designed to follow, obey and must be synchronized with a diseased organ.

Many "signals" of different nature are capable of activating endothelial cells: the shear forces created by the blood flow parallel to the surface of the vessel wall, but also forces caused by stretching perpendicular to the artery wall by the cyclic pressure gradient and the quality of these forces. The activation of endothelial cells is due to that pressurized flow dynamic forces, but also to the action of vasoactive substances and inflammatory mediators.

In this thesis we are proposing a new therapeutic approach, based on a fundamental revision of the entire systems: exposing those defects of current management of cardiovascular diseases (CVD). A concept that focuses on flow dynamics to stimulate, restore and maintain endothelial function including the heart itself. This includes preliminary results of new generations of pulsatile CAD that promote endothelial shear stress (ESS) enhancement. Devices prototypes were tested.

During this thesis, pulsatile devices prototypes were tested in vivo, in vitro as well as with pre-clinical volunteers as follow:

1. A pulsatile catheter prototype was tested in 2 pediatric animal models (piglets) of: acute myocardial ischemia; and acute pulmonary arterial hypertension.
2. A pulstile tube prototype was tested in vitro (mock circuit) and in vivo (piglets) as a left ventricular assist device (ongoing).
3. Pulsatile suit prototypes were tested: in vivo (piglets) for acute right ventricular failure treatment. Prototypes of pulsatile mask and trousers are currently in planned for pre-clinical studies.

Conclusion, Think endothelial instead of cardiac is our policy for better management of CVD.

KEYWORDS: Circulatory and cardiopulmonary failure. Shear stress. Endothelial Function. Pulsatile circulatory assist devices.

INTRODUCTION

Après plus de 60 ans de chirurgie cardiaque à cœur ouvert et 3 décennies de cardiologie interventionnelle et en dépit de leurs progrès et de leurs développements, les maladies cardiovasculaires restent la première cause de mortalité dans les pays développés [1].

La défaillance cardiaque représente la cause de mortalité la plus élevée dans les pays développés ; elle est le plus souvent liée aux maladies ischémiques avec un mort toutes les 34 secondes aux USA [2].

À l'heure actuelle la triade thérapeutique médicale, interventionnelle et chirurgicale, ne résout pas non plus le problème d'une morbidité considérable [3].

La transplantation cardiaque reste la dernière chance pour ces malades en phase terminale. Or, le nombre de donneur est de plus en plus faible [4]. L'assistance circulatoire offre une solution intermédiaire pour ce problème de manque de donneurs mais elle reste provisoire avec des inconvénients [5, 6]:

- La nécessité d'une chirurgie spécialisée offerte dans très peu de centres avec des soins postopératoires lourds et coûteux.
- Des pompes hydrauliques à galets ou centrifuges à flux continu non physiologique sont fréquemment utilisés comme assistance circulatoire. Ceci est une cause majeure de morbidité car les troubles de la fonction endothéliale dont celle de l'hémostase sont très importants.
- 80 % des assistances circulatoires sont adaptables à une surface corporelle de plus de 1.5 m^2, destinées aux patients adultes [7]. La population de patient pédiatrique rend nécessaire le développement de systèmes adaptés à leur petite surface corporelle [8].

Le concept de cette étude est fondé sur l'implication de la force de cisaillement produite par la pression rythmée du flux sanguin exercé constamment contre les parois du système circulatoire et de ses effets sur la régulation de la fonction endothéliale [9].

Conceptuellement, le système circulatoire est un circuit hydraulique, fermé, sous pression, tapissé intérieurement par des cellules endothéliales [10].

Ces forces tangentielles du stress de cisaillement (Shear stress) sont indispensables au maintien de la fonction endothéliale comprenant le tonus vasculaire par la synthèse d'oxyde nitrique (NOS), la coagulation du sang, la réponse inflammatoire, l'athérosclérose, l'angiogénèse et l'apoptose [11,12].

La fonction endothéliale est très importante puisqu'elle contrôle l'embryogénèse, la morphogénèse, l'organogénèse ainsi que le maintien d'un organisme sain [13].

Toute intervention sur ce circuit, telle que, par exemple, une pathologie ou une intervention chirurgicale, entraîne un dysfonctionnement endothélial avec des conséquences pouvant être dramatiques [14,15].

Malheureusement la plupart des stratégies thérapeutiques actuelles sont focalisées sur le cœur, en négligeant l'ensemble du système circulatoire.

Pourtant, le cœur n'est pas la seule force motrice dans notre système circulatoire [16].

Le cœur lui-même est issu de l'endothélium durant les premières semaines de gestation, à la suite de la fusion des tubes vasculaires induite par la vasculogenèse, une des multiples fonctions endothéliales dépendantes de la force de cisaillement.

Comme solution potentielle nous proposons des méthodes thérapeutiques plus physiologiques basées sur notre nouvelle théorie hémodynamique (Flux et Rythme) car toutes reposent sur des explications cardio-circulatoires.

Ainsi qu'il a été démontré expérimentalement et cliniquement, les stimulations mécaniques augmentent la production d'oxyde nitrique [17]. Ces stimulations peuvent être produites par des forces hydrauliques comme les appareils cardio-vasculaires pulsatiles.

Les appareils pulsatiles les plus utilisés sont la circulation extra corporelle pulsatile (CEC), l'assistance mécanique du ventricule gauche, le ballon de contre pulsion intra-aortique (BCPA), et la contre-pulsion extracorporelle externe (EECP) [18,19].

L'extension des applications thérapeutiques de la force de cisaillement en cardiologie est très prometteuse comme l'ont démontré les résultats de l'EECP et de la transplantation cardiaque hétérotopique en pédiatrie [20,21].

Nous ciblons notre étude sur les applications de la force de cisaillement pour préserver et stimuler la fonction endothéliale en cardiologie, et plus particulièrement chez des patients souffrant d'insuffisance cardiaque droite aigue, subaigüe ou chronique. Des patients ayant subi une CEC conventionnelle avec des troubles hémodynamiques postopératoires, ou encore des patients présentant des pathologies liées à des processus d'interdépendance « apoptose-angiogénèse » perturbés, pourraient en bénéficier aussi.

Le but de ce travail est l'extension des applications thérapeutiques de la force de cisaillement dans les pathologies cardiaques pédiatriques et adultes.

Ainsi, nous présentons ici trois systèmes pulsatiles, dont les prototypes ont été appliqués et évalués par l'expérimentation sur modèle animal incluant des explorations de la fonction endothéliale. Des études hémodynamiques et biochimiques ont été effectuées et leurs résultats comparés aux groupes de témoins traités par des méthodes traditionnelles :

Nous avons divisé nos études expérimentales en trois volets :

- Etude d'un prototype de cathéter pulsatile, testé de manière isolé dans un modèle d'ischémie aigue du myocarde et dans un modèle d'hypertension pulmonaire aigue chez le porcelet.

- Etude d'un prototype de tube pulsatile à double lumière, testé dans un circuit de CEC in vitro et in vivo comme assistance ventriculaire gauche.

- Etude d'un prototype de combinaison pulsatile, testé sur un modèle animal présentant une défaillance du ventricule droit aigue. Egalement des prototypes de masques et de pantalons pulsatiles ont été testés sur le doctorant, ainsi que ses collègues médecins volontaires à l'Université de Sun Yat Sen.

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Part I

Concept - Généralités

Chapitre I

Généralités

- *Historique*
- *Mécaniques de Fluides*

HISTORIQUE

Les maladies cardiovasculaires, qui représentent la première cause de mortalité de nos jours dans les pays développés ont attiré l'attention depuis des temps immémoriaux.

Dans l'Egypte ancienne [6, 57, 59] le cœur était un organe sacré, connu comme le centre des émotions, aussi avec des connaissances anatomiques à l'origine de vaisseaux qui distribuent les propagations pulsatiles dans le corps entier :*… du cœur naissent les vaisseaux qui vont à l'ensemble du corps … Si le médecin place ses mains ou ses doigts sur la tête, l'arrière de la tête, sur les mains, sur l'estomac, aux bras ou aux pieds, alors il examine les cœurs, parce que tous les membres possèdent des vaisseaux, c'est à dire : le cœur s'exprime par les vaisseaux de chaque membre …*

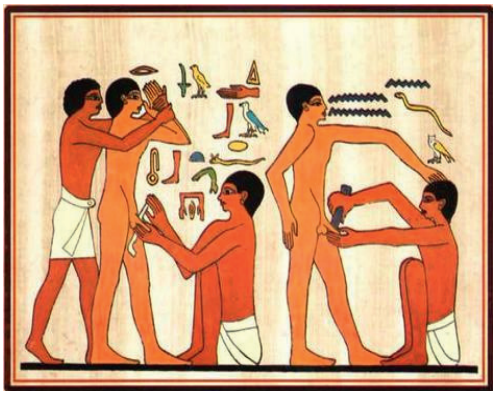
Dans leurs descriptions on peut identifier un art de l'examen clinique de précision équivalente à nos pratiques actuelles. Par exemple dans leurs citations la relation entre les pouls et l'état hémodynamique des patients *… Si le cœur tremble, a peu de puissance et chute, la maladie progresse …* ; les détails du syndrome ischémique :*... Si tu examines un homme pour une maladie de son cœur, et qu'il a des douleurs au bras, dans sa poitrine, et à côté de son cœur, ... alors tu auras à dire de celle-ci ... c'est la mort qui le menace ... Tu prépareras le stimulant des plantes médicinales …*;plus surprenant pour saluer leurs morts, en leur souhaitant tout simplement d'avoir des vaisseaux (metw) parfaits :

… Que son metw s'épanouisse ; Que son metw soit audible; Que son metw soit excellent et Que son metw soit à l'aise … .

Depuis les temps anciens en passant par la période médiévale jusqu'à la fin du XIXe siècle et au début XXe siècle, les préoccupations majeures des soigneurs ont été focalisées sur le syndrome hémorragique en cas de chirurgie ou de traumatisme.

Dans ses approches thérapeutiques, l'homme de l'art a toujours été confrontéau défide stopper l'hémorragie, qu'elle soit traumatique ou chirurgicale.

Ceci est illustré par un geste chirurgical très habile (circoncision chez l'adulte) et qui reste dangereux de nos jours avec des risques hémorragiques.



Circoncision en Égypte ancienne (2345 AC)

Les soins des blessures et des traumatismes vasculaires ont beaucoup évolués depuis l'Egypte ancienne.

Citons Ambroise Paré (1510-1590), qui a notamment contribué aux principes de bons soins des plaies, qu'il a également appliqué aux opérations de l'anévrisme.

La transfusion sanguine était le rêve absolu des soignants, tentée notamment en avril 1492 pour le Pape Innocent VIII qui a été transfusé par de trois jeunes garçons, avec des résultats catastrophiques : décès des quatre personnes impliquées.

En 1628, Giovanni Colle, médecin italien, a effectué la première description concise d'une transfusion sanguine [30].

Transfusion du sang, Giovanni Colle (1628)

Les résultats des tentatives de transfusion ont été rares et dangereuses par la suite, jusqu'à la découverte des groupes sanguins en 1900, ce qui a résolu le problème des réactions fatales.

En 1902, Karl Landsteiner [38], a montré l'existence de trois puis quatre groupes sanguins dans le système ABO. Les découvertes par la suite des anticoagulants, premièrement le citrate de sodium (1914), suivi par la découverte de l'héparine en 1916 par Mclean et Howell.

Nous considérons cette aventure douloureuse parmi les plus glorieuses de l'histoire de la médecine, en maintenant avec acharnement le bon concept en dépit des échecs successifs pendant des siècles, jusqu'à la maîtrise théorique et pratique de cette voie thérapeutique.

Résoudre les craintes d'une hémorragie n'a pas pour autant aidé à l'approche de la chirurgie cardiovasculaire.

Des progrès sur *les moyens diagnostiques* se sont succédés sur plusieurs siècles. Citons brièvement parmi quelques moments glorieux :

Les *mesures de pression* artérielle ont été marquées par le révérend Hales (1733) qui a mesuré la pression artérielle selon la hauteur d'une colonne du sang éjectée dans un tube de bambou implanté dans le carotide d'un cheval.

Suivi par l'invention du Sphygmomanomètre en (1881) par Karl Ritter von Basch et le « windkessel »,à l'origine des moniteurs cardio-pulmonaires, par Otto Frank (1899) [29, 50].

Révérend Stephen Hales (1733)

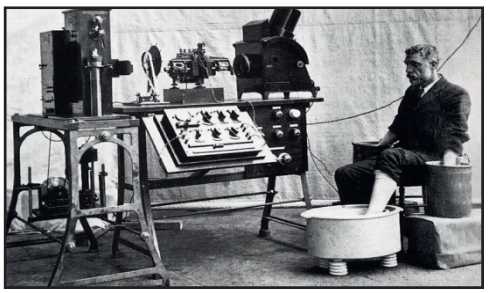
L'Auscultation cardiaque qui à été démarré par l'invention du stéthoscope par Laennec (1816), suivi par des modifications plus pratiques dont celles de Rappaport et Sprague (1941) [50].

Laennec (1816)

L'*électrocardiogramme* (ECG) basé sur le concept du Matteucci (1842) en montrant que chaque contraction du cœur s'accompagne d'un courant électrique [26].

L'ECG qu'a étéinventé par Einthoven en (1902) en utilisant à la fois deux précédentes inventions françaises :

L'électromètre capillaire inventé par Lippmann en 1872 et le galvanomètre à corde de Clément Ader (1897).



« ECG » Sir Thomas Lewis (1912)

A l'exception des quelques procédures vasculaires, les développements thérapeutiques se sont limités aux méthodes diagnostiques et aux traitements médicaux, dont l'importante découverte des « Nitrates » pour traiter l'angine de poitrine par Thomas Brunton en 1878[1].

L'*angiographie – coronarographie :*les premières tentatives sur le concept de la radiologie de contraste ont été effectuées par Moniz (1927) en neurologie, suivi par l'incroyable démonstration de Forssmann (1929) qui n'a pas hésité à cathétériser et photographier son propre ventricule droit par un cathéter veineux.

Dans le début des années 1940, Cournand, en collaboration avec Richards, ont effectué des mesures hémodynamiques du cœur [8].

Tous ont été honorés par le prix Nobel : Moniz (1949), Forssmann [21], Cournand, Richards (1956), pour leurs travaux dans la découverte du cathétérisme. Les évolutions ont été marquées par l'approche percutanée aujourd'hui largement utilisé et développé par Seldinger en 1953 [53].

Sones, en 1958, a effectué par hasard la première coronarographie chez un patient en souhaitant injecter de manière rétrogradeun produit radio opaquedans le ventricule gauche [55].

Ceci a été à l'origine de la cardiologie interventionnelle démarrée par Dotter et Judkins (1964), pour le traitement d'un patient atteint d'une maladie athéromateuse de l'artère fémorale superficielle gauche [15].

William Rashkind est considéré comme le père de la cardiologie interventionnelle. Il a effectué à Boston en 1966, la première septostomie atriale par ballon pour soulager les enfants atteints de transpositions des gros vaisseaux.

Le premier succès de l'intervention coronaire percutanée (PCI) avec un ballon-cathéter a été obtenu par Gruentzig (1977), suivi par le premier stent coronaire par Puel et Stigwart en 1986[27].

Les méthodes diagnostiques non invasives ont été marquées par le développement del'échocardiographie en mode M, décrite par Edler le «père de l'échocardiographie » et Hertz en 1953, comme une nouvelle technique non invasive pour le diagnostic de pathologies valvulaires [51]. Ceci a été suivi par le développement de l'échographie Doppler bi-dimensionnelle, de contraste et l'échographie trans-oesophagienne.

Le scanner : son concept a été conçu par Hounsfield en 1967 et annoncé publiquement en 1972 [47].

L'Imagerie par Résonance Magnétique (IRM), est une nouvelle technologie qui a été publiée en 1973 [40].

Évènements historiques de la chirurgie cardiaque:

Les premières tentatives pour aborder le cœur chirurgicalement, ont été confrontées à des difficultés techniques liées aux voies d'abords aboutissant à des innovations pour les instruments, les médicaments ainsi que les appareillages pour assister le cœur pendant et après l'intervention.

Ceci n'a permit que le développement de la chirurgie à cœur fermé, comme la suture des plaies cardiaques réalisée pour la première fois par Ludwig Rehn [46], à Francfort en 1896. Suivirent des pionniers comme Vineberg qui a implanté une artère mammaire interne directement sur le myocarde [58].

Ceci a ouvert la porte au pontage coronaire sur cœur battant qui a été réalisé par Kolesov au début des années soixante [35].

Pour la chirurgie valvulaire, une commissurotomie mitrale sans CEC a été effectuée par Bailey en 1948 [3].

La réparation des malformations cardiaques a été démarrée par Gross, en 1939, par la ligaturedu canal artériel [25].

Quelques années plus tard (1943), à l'aide des techniques développées par Vivien Thomas, Alfred Blalock réalise un shunt entre l'artère sous-clavière et l'artère pulmonaire droite sur le concept de Madame Taussing [4].

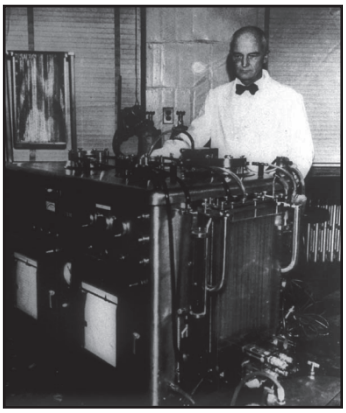
Ensuite vint la section et réparation des coarctations aortiques, en 1944 par Crafoord à Stockholm [5,10].

En parallèle plusieurs groupes ont essayé le remplacement total ou partiel du cœur pendant l'intervention cardiaque : Michael DeBakey du Texas Heart Institut, a développé un système de pompe de perfusionau début des années 30, et ouvert ainsi la porte à la chirurgie à cœur ouvert qui se développera quelques décennies plus tard [16].

L'introduction de la circulation extracorporelle (CEC) a été réalisée par Gibbon [23,24], la première fois en 1953, ce qui a démarré l'ère de la chirurgie cardiaque à cœur ouvert. La CEC a été améliorée remarquablement par la suite notamment par John Kirklin [33,34], à la Mayo Clinique dans les années cinquante.

L'assistance cardiaque a été complétée par l'introduction du premier cœur artificiel implanté chez l'homme en 1969 par Cooley [11], et Liotta [43], l'auteur du concept appliqué chez les chiens depuis 1961.

Le Dr Adrian Kantrowitz, le chirurgien qui a effectué la première transplantation cardiaque chez l'homme aux Etats-Unis, développel'utilisation de plus de 20 dispositifs médicaux,d'assistance cardiaque, dontle ballon de contre pulsion aortique (Intra-aortic balloon pump IABP), le dispositif d'assistance ventriculaire gauche (LVAD), et unepremière version du défibrillateur implantable [36,37].



Dr. Gibbons (CEC-1953)

La chirurgie cardiaque à cœur ouvert, nous a emmené dans le nouveau domaine de la protection myocardique, en commençant par le froid.

L'arrêt cardiaque effectué par le froid par la machine de CEC, ou de liquides froids dans le péricarde selon la technique de Shumway, qui nous a permis de travailler à cœur fibrillé, a été révolutionnée par l'introduction de la cardioplégie en injectant des perfusions cristalloïdes froides enrichies en potassium dans les ostia coronaires.

La protection cardiaque a été améliorée par plusieurs équipes dont des institutions parisiennes (Broussais,Lariboisière).

Il a fallu comprendre et soigner le cœur souffrant après l'arrêt chimique : le syndrome de reperfusion (reperfusion injury) a été décrit par Cooley en 1969 (the Stony Heart). Et, l'implication des radicaux libres a été explorée à la fin des années quatre-vingt au laboratoire A Carpentier à l'Hôpital Broussais [12-14].

Malheureusement l'amélioration des méthodes de protection myocardique n'a pas complètement résolu les effets secondaires de la CEC, surtout en flux continu.

Ces progrès effectués dans l'innovations des appareillages diagnostiques ont été accompagnés par des découvertes révolutionnaires dans les domaines biologiques et histo-pathologiques cardiovasculaires.

Celles-ci ont été marquées par la grande découverte de la fonction endothéliale par Furchgott en1978, et le rôle du monoxyde d'azote (NO) ou EDRF (endothelial-derived relaxing factor) dans sa première description, un composé important dans de nombreux aspects de la physiologie cardiovasculaire.

Ceci a permis de détailler le postcardiotomy syndrome : troubles hémodynamiques, troubles de l'hémostase, syndrome inflammatoire, l'apoptose, … etc, éléments du syndrome de dysfonctionnement endothélial.

Par conséquent la chirurgie cardiaque qui n'a cessé de progresser depuis les années cinquante jusqu'au fin des années quatre-vingts, marquent le pas depuis deux décennies.

Au « Texas Heart Institut », Denton Cooley a mis au point d'importantes techniques innovatrices ; Stanley Crawford fut un des pionniers de la chirurgie de l'aorte thoracique. Demikhov en Russie [17,18] et Shumway à Stanford University [42], ont développés séparément la technique de transplantation cardiaque et cardiopulmonaire au début des années soixante chez les chiens, technique appliquée par Christian Barnard en Afrique de Sud après un séjour à Stanford [7].

A la Mayo Clinic, McGoon [44] et son équipe ont marqué l'histoire de la chirurgie cardiaque pédiatrique ; à l'hôpital Johns Hopkins, Alfred Blalock a réussi la première intervention cardiaque à cœur ouvert sur une Tétralogie de Fallot (TOF) en hypothermie en 1952, aidé par son élève Lillehei [39]. Lillehei a developpé en 1958 son concept du premier pacemaker portable, fabriqué à sa demande par Earl Bakken, fondateur de Medtronic. A Oregon, Starr a mis au point la première valve mécanique [56]. A Boston (Harvard) Aldo Castaneda a développé la réparation congénitale chez les nouveaux nés ; il faut également citer les grands cardiologues Eugene Braunwald et William Rashkind, un grand morphologiste Van Praagh.

A partir des années soixante la chirurgie cardiaque a été renforcée par la participation des grandes institutions européennes et mondiales : National Heart Institut de Londres avec Doland Ross [48,49], qui a mis au point, parallèlement avec Barratt Boyes en Nouvelles Zélande, la technique d'implantation des homogreffes aortique et pulmonaire. Dans plusieurs institutions londoniennes, dont celui du Royal Brompton Hospital (Lord Brock) a effectué la première commissurotomie mitrale à cœur fermé [2]. Au sein de la National Heart Institut, Sir Yacoub a révolutionné la

chirurgie cardiaque pédiatriqueen réalisant la première réparation anatomique de transposition de gros vaisseaux (TGV) [32].

Egalement, les groupes de Great Ormond Street (Stark et Deleval), ont contribués au développement de la chirurgie cardiaque pédiatrique.

En France, à l'Hôpital Broussais de Paris, lePr. Alain Carpentier a mis au point ses techniques innovatrices de la réparation mitrale, ainsi que la première bio-prothèse valvulaire développée dans les années soixante et la première cardiomyoplastie en 1985[19].

A Laennec : Yves Lecompte avec sa technique révolutionnaire pour la réparation TGV [41]. Claude Planché[45], a amené l'hôpital Marie-Lannelongue parmi les plus grands centres au monde de chirurgie cardiaque pédiatrique. A Bordeaux, Fontan[22] et Baudet mettent au point leur intervention pour l'atrésie tricuspide. En Suède à l'Institut Uppsala : Bjork invente la valve mécanique à mono disque. En Suisse : Senning a une technique audacieuse pour la réparation de TGV à l'étage atrial [54].

En Argentine Liotta, le père du cœur artificiel, Favalaro [20], qui a réalisé le premier pontage coronaire avec une veine saphène en 1966 aux USA.

Cette partie passionnante de l'histoire de la médecine est traitée dans plusieurs ouvragesremarquables. [9,28,31,52].

Nous avons résumé très brièvement quelques moments phare de cette histoire, en rendant hommage aux hommes patients et soigneux à la fois, en mentionnant peu de références scientifiques car la plupart sont devenues des notions connues des non-spécialistes.

Le rapport entre l'Homme et son cœur, depuis le temple des Pharaons, aux médecins initiés sur le sacré, jusqu'aux chirurgiens et cardiologues interventionnels de la deuxième moitié du XX^{ème} siècle, en passant par les biologistes et des ingénieurs biomédicaux.

Le concept historique de l'Égypte ancienne sur la propagation de la pulsation du cœur aux vaisseaux sanguins, est proche de notre théorie « Flux et Rythme », reconnu comme l'origine du développement du corps.

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MÉCANIQUE DES FLUIDES

Physique et Médecine sont des sciences interdépendantes, car on peut considérer le système circulatoire comme un circuit fermé sous pression hydraulique, qui obéit aux lois de la physique. Nous devons beaucoup aux spécialistes du génie biomédical, sans eux aucun progrès ne serait réalisé dans notre spécialité.

Nous citerons très brièvement les principes théoriques et lois physiques qui influencent directement et indirectement le système circulatoire :

Pascal (1659):Dans une colonne hydrostatique, la pression est une grandeur scalaire où le fluide exerce une force par unité de surface dans toutes les directions. Bien qu'elle soit considérée comme une loi hydrostatique, elleest appliquéeen cardiologie pour mesurer la pression artérielle par le tensiomètre en utilisant des colonnes de mercure (Hg). Où: 1 mm Hg = 13,6 mm d'eau = 1332 dynes/cm^2 = 0,018 psi (livres par pouce carré)[1].

Newton (1668) :C'est la loi de viscosité ou de Shear stress. Un liquide dans un circuit hydraulique fermé est soumis à la force de friction tangentielle par unité de surface (force de cisaillement pariétale) et à la force de distension perpendiculaire (pression du liquide).

La viscosité du fluide Newtonien (μ), est constante et indépendante du taux de cisaillement.

Cette loi de Newton et ses dérivationscomme l'équation Navier–Stokes, sont appliquées dans nos appareils échocardiographiques doppler et dans nos scanners pour les mesures hémodynamiques du flux sanguin [2].

Bernoulli (1738) : La différence de pression entre deux points correspond à la différence de perte d'énergie aux frontières.La loide Bernoulli est la base de tous les moniteurs de pression cardio-pulmonaire, depuis l'introduction du Wendkessel par Otto Frank en 1899. Ces équations sont les plus fréquemment appliquées dans les systèmes hydrauliques du génie. Quelques formules équivalentes sur la base des principes de Bernoulli en particulier la troisième équation, certains d'entre eux sont de Fourier, d'Ohm, Shepard, Fickes, etc[3].

Nombre de Reynolds (1880) : Le nombre de Reynolds représente le rapport entre les forces d'inertie et les forces visqueuses.L'écoulement du fluide se divise en trois types de flux selon Reynolds: Flux laminaire Re<2000, flux transitionnel Re 2000 – 4000) ou Flux turbulent Re>4000.

Les effets de ce principe de Reynolds s'appliquent à la formation des plaques d'athéromes dans les zones du flux turbulent. Autre exemple, nous pensons que le succès de l'applicationde la normothermie pendant la CEC aun lien directe avec le nombre de Reynolds car le sang devient un liquide Newtonien ce qui diminue les troubles del'hémostase[4].

Laplace : La loi de Laplace décrit la relation entre la différence de pression transmurale et la tension, le rayon, et l'épaisseur de la paroidans un récipient cylindrique.La paroi des vaisseaux sanguins est tendue en raison de la différence entre la pression artérielle à l'intérieur du vaisseau et la pression ambiante à l'extérieur. Par exemple, dans les cardiomyopathies dilatées, le cœur devient très distendu et le rayon ventriculaire (r) est augmenté. Ainsi dilaté,le cœur exige plus d'énergie pour pomper la même quantité de sang par rapport au cœur de taille normale. Ceci est appliqué dans la nouvelle théorie sur le remodelage ventriculo - vasculaire. Les applications des principes de Laplace peuvent améliorer le fonctionnement des cœurs défaillants dilatés [5].

Hagen - Poiseuille : Qui décrit l'écoulement laminaire (c'est-à-dire à filets d'eau parallèles) d'un liquide visqueux dans unconduit cylindrique.
Pourtant, son application théorique en cardiologie est impossible vu la variabilité de l'élasticité et des vaisseaux, sa présence est considérée comme le filtre artériel pour les amorçages des flux turbulent [6].

Séparation de la couche limite:À la limite où la direction du fluide change de vitesse, elle créera une ligne de résistance appelée ligne de vortex, opposée à leur direction. Ces tourbillons deviennent de plus en plus turbulentsentraînant des pertes d'énergie très importante dans le flux (momentum energy losses).

Flux divergent "gradient de pression positive » :

Un diffuseur divergent provoque un flux turbulent avec des pertes de charges importantes(Figure ci-contre 9A).Selon le principe de Bernoulli, un conduit divergentest un flux croissant conduisant à la réduction de la vitesse (V) engendrant une augmentation de la pression (P) : P1<P2 et V1>V2.

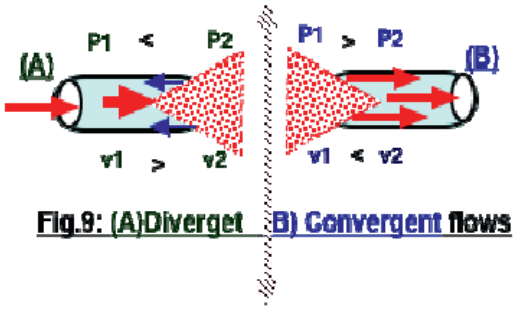

Fig.9: (A)Diverget (B) Convergent flows

Lorsque la pression (P)augmente dans le sens du débit (vers le centre), le fluide à l'extérieur de la couche stagnante vers la paroiprovoque une résistance avec une pression vers l'arrière(flèches bleues)[7].

Flux convergent "gradient de pression négative" (Figure ci-contre 9B):

Un diffuseur convergent reçoit moins de turbulences avec faible perte de charges.P1> P2 et V1 <V2 (P = pression, V = vitesse).Lorsque la pression diminue, au sens d'écoulement du fluide cela permet d'accélérer le maintien du flux à la paroi, avec le moindre turbulence et vortices [7].

L'effet de Fahraeus-Lindquist:

Sur la base de la pression de Bernoulli, l'effet Fahraeus-Lindquist (schéma ci contre) décrit le flux sanguin dans la microcirculation. Le principe d'un fluide en mouvement est diminué par sa composante cinétique, plus le liquide se déplace, plus faible sera la pression hydrostatique.En clinique, le sang est moins visqueux quand le diamètre vasculaire diminue.La viscosité est indépendante du rayon du vaisseau pour un fluide Newtonien comme le plasma.

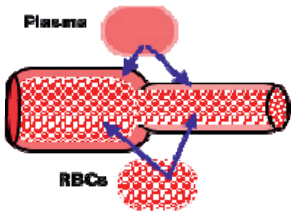

Fig. 7:Fahraeus-Lindquist

Dans les petits vaisseaux les forces des cisaillements d'après la loi de Bernoulli, attirent les globules rouges vers le centre du vaisseau sanguin où la vitesse est la plus forte et donc la pression est plus faible.

Lorsque le fluide en faible viscosité comme le plasma reste bloqué à la paroi où la plupart des vortex se produit.

Frank-Starling (loi du cœur) :L'augmentation progressive de la contractilitécardiaquedépend du remplissage télédiastolique ventriculaire. Cependant, au delà des conditions optimales de contraction du ventricule, la force de contraction va diminuer.

Le cœur ajuste son débitau fur et à mesure de la précharge ventriculaire droite [9].

Starling (loi de capillaire) : Ce qui explique la circulation du fluide dans les capillaires entre les artérioles et les veinules.

Il ya un certain nombre de force agissant à la force de fluide à travers les cellules endothéliales des capillaires. On comptabilise la pression artérielle (pression hydrostatique), la protéine plasmatique, la pression osmotique, la gravité et l'élasticité tissulaire [9].

En résumé

L'écoulement du fluide à travers un circuithydraulique est directement proportionnel à la pression motrice et inversement proportionnelle à la résistance du circuit. Une pompe est un modèle mathématique d'un système physique, en considération des lois telles que la mécanique des fluides,pour conduire un liquide Newtonien et incompressible dans un circuit hydraulique avec des parois fixes et rigides.Celle-ci, représente une telle difficulté in vivo en raison de élasticité des vaisseaux et variétés géométriques vasculaires. En plus, le sang est considéré comme un fluide non-newtonien, en raison de sa viscosité inconstante.

Nous croyons que la viscosité du sang est variable pour faire face à chaque situation hémodynamique, par exemple : l'embryogénèse, la cardiopathie cyanogène, etc.

L'endothélium qui contrôle la viscosité du sang et les résistances vasculaires joue un rôle important pour maintenir l'écoulement du sanget les forces hémodynamiques (Flux et Rythme).

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Chapitre II

« Flux et Rythme » : *Concept et observation hémodynamique*

HÉMORRHÉOLOGIE - FONCTION ENDOTHÉLIALE

Conceptuellement, le système cardio-vasculaire est un circuit hydraulique, fermé, sous pression (schéma 1), tapissé intérieurement par des cellules endothéliales. Le fonctionnement de ces cellules endothéliales est régulé par la pulsation cardiaque qui entraîne des variations de pression dans les vaisseaux et donc un cisaillement de ces cellules, ce qui les stimulent. Ces forces tangentielles du stress de cisaillement (Shear stress) sont indispensables au maintien de la fonction endothéliale comprenant le tonus vasculaire par la synthèse de monoxyde d'azote (NOS), la coagulation du sang, la réponse inflammatoire, l'athérosclérose, l'angiogénèse et l'apoptose. La fonction endothéliale est très importante puisqu'elle contrôle l'embryogénèse, la morphogénèse, l'organogénèse ainsi que le maintien d'un organisme sain [1-3].

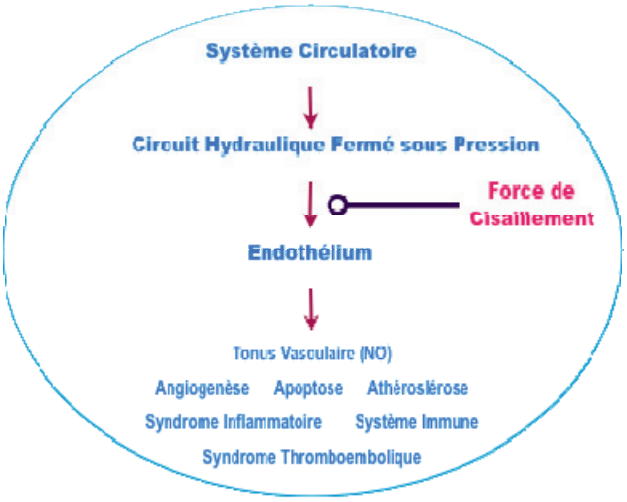

Schéma 1: Principes biophysiologique du Système Circulatoire.

Flux et Rythme *et développement du cœur et vaisseaux* (Figure 1) **:**

L'angiogénèse est l'une des multiples fonctions de l'endothélium. L'angiogénèse joue un rôle clé dans les processus de l'embryogenèse, de la morphogenèse, de l'organogenèse, et de la cicatrisation des plaies.

Vers le 6ème jour de gestation, l'angiogénèse placentaire prépare l'implantation embryonnaire dans l'endomètre, stimulée par les forces hémorhéologiques maternelles (conditionnées par une bonne pression artérielle et hématocrite).

Autour du 8ème jour de gestation commence la vasculogenèse contrôlée par les forces de cisaillement et les facteurs neuro-humoraux maternels.

Ce processus d'angiogénèse est nécessaire à la construction de l'ensemble du système cardio-vasculaire, que nous devrons appeler le système *Cardioendothélial* car l'endothélium est à l'origine du cœur et des vaisseaux [4-7].

Vers le 21ème jour survient le premier battement cardiaque en même temps que les deux vestibules auriculaires et oculaires [8]. À vrais dire, ce cœur du fœtus n'intervient pas au processus métabolique pendant la vie intra-utérine qui est assuré par la circulation placentaire.

Autrement dit, le cœur du fœtus peut-être considéré comme un générateur de la force de cisaillement afin de stimuler la fonction endothéliale (*la première assistance circulatoire biologique*).

Les apparitions des centres auriculaires et oculaires au même temps du premier battement cardiaque jouent un rôle décisif dans le processus de l'embryogénèse**.** Car il est fort probable la présence des récepteurs qui se lient entre l'oreille, l'œil, le cœur et des senseurs endothéliaux.

Ces récepteurs sont responsables aux démarrage du premier battement cardiaque par des facteurs neuro-humoraux et mécaniques maternels sur l'endomyocarde de l'oreillette droite [9].

En effet le fluide amniotique augmente la propagation des ondes sonores des battements cardiaques maternels, qui seront distingués de son propre battement cardiaque par le fœtus grâce aux récepteurs créés dans le vestibule auriculaire.

Plusieurs facteurs hémorhéologiques favorisent l'effet de cette force de cisaillement sur l'endothélium du fœtus à savoir un rythme cardiaque très élevé d'environ de 285 bpm au premier trimestre, des globules rouges morphologiquement, plus larges en volume et dimensions afin de bien capter et adhérer aux oxygènes placentaires. Ces derniers augmentent leur effet de cisaillement sans changer la viscosité sanguine.

Le sac amniotique qui joue un rôle protecteur en empêchant l'intervention des autres facteurs stimulants des organes voisins: comme la gravité ou les propagations externes des forces pulsatiles maternelles : l'aorte abdominale, la motilité viscérale, etc.

Toute perturbation de ces facteurs hémorhéologiques peut nuire au processus de l'embryogénèse et menacer la continuité de la grossesse aussi bien chez le fœtus comme chez la mère. À titre exemplaire, une bradycardie peut-être fatale chez le fœtus, une pré-éclampsie, les traitements anticoagulants, les antihypertenseurs ou encore les effets secondaires du flux continu de CEC durant une intervention cardiaque [10].

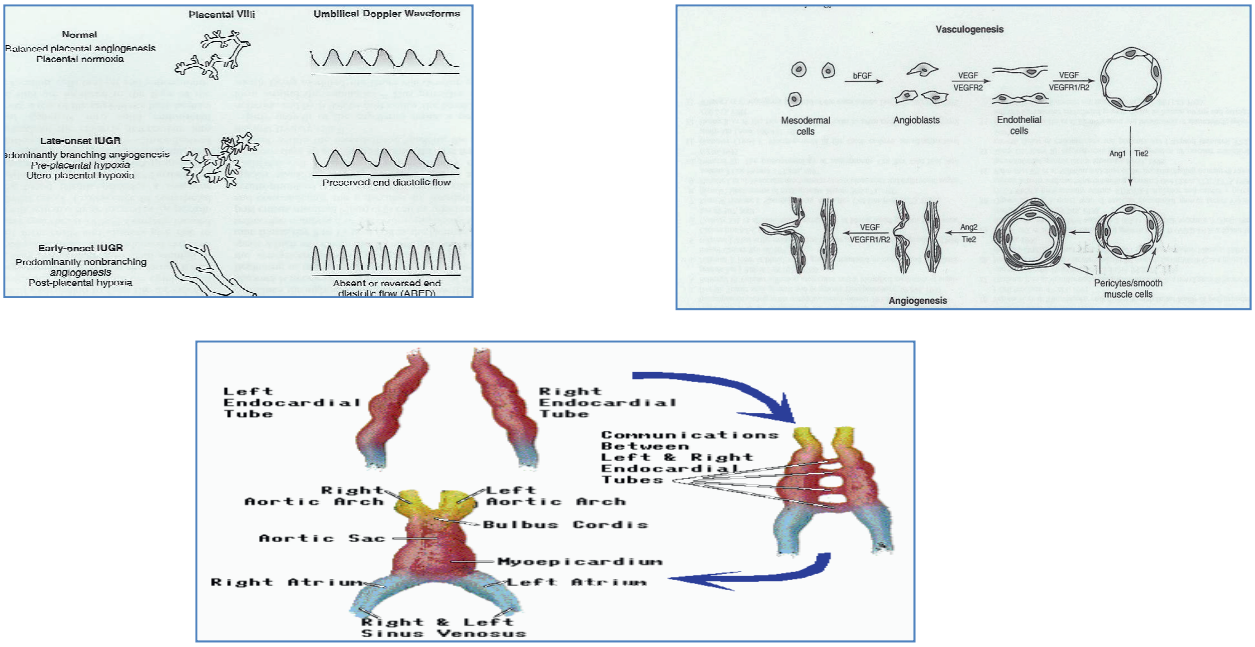

Figure 1: développement de système circulatoire (Fœtus)

Images : haute à gauche = angiogénèse placentaire; haute droite : casculiogénèse; et en bas au centre : cardiogénèse [6].

Exemples et observations physiopathologiques :

Celle-ci est visible en pratique sur l'effet des ondes soniques sur le battement cardiaque, ce que stimulent des récepteurs de catécholamines contrôlés par l'endothélium, comme l'effet reposant ou stimulant de la musique. Le phénomène, qui lie l'étonnante observation : un nouveau-né qui se calme par des bruits très forts comme ses habitudes dans sa vie anténatale.

La bradycardie produite par la pression oculaire qui est pratiquée plus souvent par les réanimateurs devant un tableau de tachyarythmie, est un autre exemple montre le lien physiologique entre le cœur, l'œil [11].

Ainsi des nombreuses études ont montrées les associations des malformations congénitales avec la perturbation du fluide amniotique [12]. Notamment une étude réalisée par la NASA consistant à évaluer les effets de la gravité et la pression atmosphérique dans l'espace sur la grossesse chez les souris. Elle a démontré que les souris ont accouchés normalement sans aucune malformation sauf une courte période de vertige, car les mamans sous l'effet de la pression atmosphérique et de la gravité supprimée ont transmis leurs facteurs neuro-humoraux aux fœtus qui a été protégé par le sac amniotique des effets secondaires directe de l'espace [13,14].

Flux et rythme et shunts physiologiques

Au cours de la vie intra-utérine en effet, bien que le ventricule droit (VD) reçoive 2/3 du volume sanguin corporel, les parois des veines et du ventricule droit gardent un remodelage bas par rapport aux artères systémiques en raison de l'existence de shunts physiologiques (ductus venosus, canal artériel, foramen ovale).

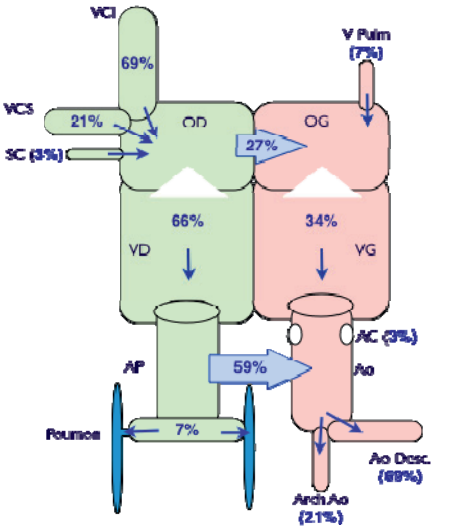

Schéma 2: Distribution du flux sanguin chez le fœtus de brebis (Nour)

Dans une représentation de la circulation du fœtus chez le Brebis (schéma 2), qui montre la distribution du flux sanguin par le cœur effectuée en plusieurs petits circuits fermés, parallèles et équilibrés: le volume sanguin de la veine cave inférieure (VCI) est égal du retour par l'aorte ascendant (69%); pareillement le flux coronaire (AC) est égal de celui du sinus coronaire (3%) ; la veine cave supérieure (VCS) = le débit dans l'arche aortique (Arch. Ao = 21%); les flux équilibré entre l'artère pulmonaire et les veines pulmonaires (7%). Les deux shunts physiologiques qui participent à la distribution du flux sont la communication inter auriculaires et le canal artériel avec 27% et 59% du volume sanguin respectivement.

Toute perturbation de cette distribution du volume sanguin peut entrainer des malformations congénitales [15].

FLUX ET RYTHME en période postnatal

En période postnatale le cœur commence à prendre son rôle physiologique, après la suppression de la circulation placentaire, la chute de la résistance pulmonaire, fermeture des shunts, ainsi que le ventriculaire gauche triple presque sa masse dans un délai d'un mois.

Après la naissance et en raison de la fermeture des shunts physiologiques chaque ventricule reçoit le même volume sanguin qui sera éjecté avec la même fréquence. Soumis à des conditions rhéologiques identiques le ventricule droit ne représente pourtant que 1/6 de la masse myocardique du ventricule gauche (VG).

Le cœur et les forces péristaltiques artérielles représentent les forces circulatoires principales qui poussent le flux sanguin de façon pulsatile avec une pression différentielle (pulse pressure) dans le réseaux artériel.

Contrairement au cœur gauche, le circuit veineux et lymphatique, le flux sanguin s'écoulent de façon continue sous l'action de forces circulatoires de différentes natures indiquées dans le: mouvements respiratoires (diaphragme, muscles intercostaux), pompe musculaire, gravité, pression atmosphérique, récepteurs cutanés, viscosité, intervention du cœur droit (valves, oreillette, ventricule, pression pulmonaire, capacitance veineuse, péricarde).

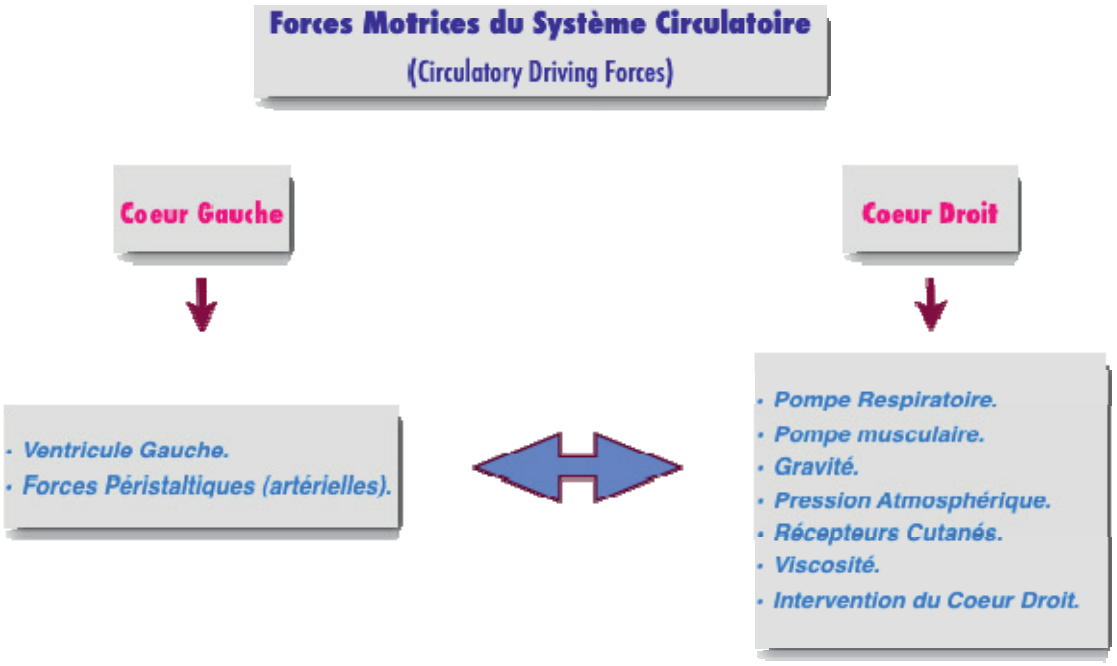

Schéma 3: Forces Motrices du système Circulatoire en période postnatale (Nour)

ANATOMIE CARDIOVASCUALIRE ET FACTEURS BIOPHYSIQUES

I- *Le Cœur Gauche* :

Le circuit du cœur gauche (Schéma 4), se divise principalement en deux parties : une pompe ventriculaire (VG) aidée par la force péristaltique aortique et artérielle. La forme sphérique et la masse musculaire du VG permettront l'injection d'un volume sanguin avec une pression quasi constate dans tout le circuit artériel (volume d'éjection systolique). Les résistances vasculaires systémiques (la postcharge) qui est contrôlées par des médiateurs vasodilatateurs sécrétés par l'endothélium.

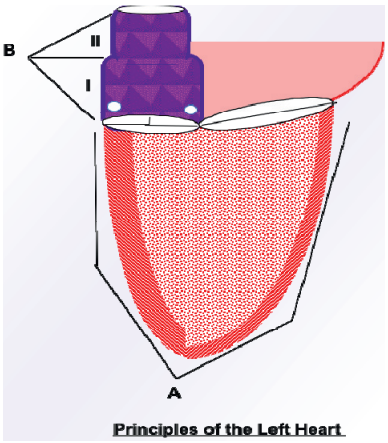

Schéma 4: Principes biophysiologique du cœur gauche. A= ventricule gauche : B=aorte (II) et Valsalva (I). (Nour)

Le sinus de Valsalva correspond à une dilatation de la racine de l'aorte, située au dessus des trois valvules sigmoïdes aortiques.

Le sinus de Valsalva joue des rôles hémodynamiques et physiopathologiques importants dans ce circuit du cœur gauche. Par exemple, un renforcement de la pression systémique s'effectue par l'accumulation des colonnes sanguines dans le Valsalva et qui seront éjectées à la fin de systole après la fermeture de la valve aortique, (dicrotic wave) [16].

Egalement les deux artères coronaires (droite et gauche), naissent au niveau de deux de ces dilatations. Le développement coronaire s'effectue suite au déplacement de la colonne du sang en amont et en aval dans le sinus de Valsalva afin de creuser les ostia aux endroits les plus affectés et exposés [17].

Les anomalies coronaires sont les plus souvent associés aux malformations conotroncales dont le rapport entre le Valsalva et le niveau étagère valvulaire aorto-pulmonaire sont mise en cause [18,19].

La bicuspidie aortique qui représente presque 20% des anomalies cardiaques se manifeste à l'âge adulte par une sténose aortique calcifiée et serrée. Cela un effet directe de la perturbation et vortices du flux au niveau de la racine aortique avec le manque de Valsalva bien développé [20].

II- *Le Cœur Droit* :

En principe, le cœur droit domine le développement et l'hémodynamique du cœur gauche depuis la vie anténatale en maîtrisant le *Flux sanguin et le Rythme cardiaque*.

Au cours de la vie intra-utérine en effet, bien que le ventricule droit (VD) reçoive 2/3 du volume sanguin corporel, les parois des veines et du ventricule droit gardent un remodelage bas par rapport aux artères systémiques en raison de l'existence de shunts physiologiques (ductus venosus, canal artériel, foramen ovale).

Après la naissance le cœur droit qui contient presque 64% du volume sanguin dans ses capacitances veineuses, garde toujours un remodelage bas malgré l'égalité des forces héméorhéologiques exactement à gauche comme à droite après la fermeture des shunts physiologiques.

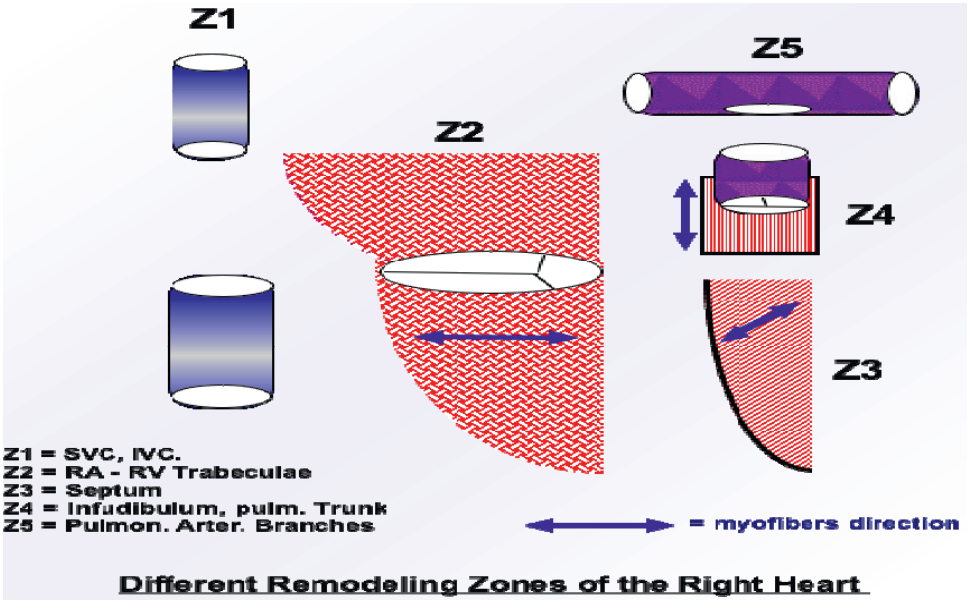

Schéma 5: Principes biophysiologique du cœur droit divisé en 5 zones (Z) de remodelage. IVC, SVC= veine caves inférieure et supérieure; RA-LV= oreillette et ventricule droites ; pulmon Arter = artère pulmonaire . (Nour)

Ceci s'explique en raison de deux facteurs majeurs :

A) <u>Cardiaque</u> :

En dehors des caractéristiques déjà décrites dans la littérature [21], nous insistons sur le rôle majeur joué par le muscle trabéculaire qui tapisse l'intérieur de la face antérieure de l'oreillette droite et la plus grande partie de la cavité ventriculaire (hormis le septum et l'infundibulum).

Le principe sur lequel se base la présente théorie permet de diviser le cœur droit en cinq zones morphologiques (Schéma 5).

Ces cinq zones des différents remodelages selon la réponse aux forces de cisaillement effectuées sur les parois endothéliales sont les suivantes (schéma 5):

- **Zone 1**: représentée par le système veineux, faiblement remodelée en raison de l'absence de forces rythmiques. Le flux sanguin s'écoulant en basse pression dans cette zone est sous l'influence des forces circulatoires accessoires (Schéma 3).
- **Zone 2**: représentée par la cavité atrio-ventriculaire, où le flux sanguin de retour veineux commence à s'animer (rythme et pression) ce qui entraîne un remodelage modéré. Le muscle trabéculaire joue ici un rôle de frein naturel atténuant les forces des cisaillements exercées sur la paroi ce qui permet à celle-ci de se contenter d'une épaisseur de 1/6 de celle du ventricule gauche (qui ne possède pas une importante zone trabéculaire). Dans cette zone l'hémodynamique dépend du remplissage diastolique (la précharge) indispensable pour nourrir le muscle ventriculaire droit surtout dans sa partie trabéculée.
- **Zone 3**: C'est le septum inter ventriculaire qui garde une morphologie normale à gauche comme à droite, liée à sa vascularisation par les artères inter septales. L'hémodynamique de cette zone dépend indirectement de celle du ventricule gauche (vascularisation commune) et directement des forces de cisaillement s'exerçant à droite afin de baisser la postcharge pulmonaire (ce qui entraînera une amélioration hémodynamique consécutive à gauche).
- **Zone 4**: représentée par l'infundibulum avec un remodelage très élevé conséquence de l'importance des forces de cisaillement renforcées par une vascularisation directe par la première artère interseptale.

L'hémodynamique de cette zone dépend donc des forces de cisaillement (volume et rythme) et de la surcharge de pression de la première artère inter septale.

- **Zone 5**: représentée par l'arbre pulmonaire artériel, zone peu remaniée, avec un pourcentage diamètre-épaisseur de paroi quasi identique à celui des grandes veines. L'hémodynamique de cette zone dépend des résistances vasculaires (baisse de la postcharge), elles-mêmes liées aux forces de cisaillement (surtout le rythme car l'arbre arrive à baisser sa pression artérielle, grâce à sa compliance, bien qu'il reçoive le même volume sanguin que l'aorte.

B) <u>Extracardiaque</u> :

La fluctuation et la propagation des ondes pulsatiles externes peuvent réagir comme une force des cisaillements extravasculaires avec une stimulation de la fonction endothéliale.

La pompe respiratoire « Maître» du système circulatoire:

Sous le contrôle des forces accessoires détaillées (Schéma 3). Nous considérons en particulier que la pompe respiratoire possède un effet direct sur le contrôle physiologique du système circulatoire.

A la manière d'un « Accordéon » les mouvements d'inflation / déflation des poumons créent une force de cisaillement externe sur les vaisseaux pulmonaires. Leurs effets impressionnants démarrent après la naissance à la première inspiration, qui entraîne une baisse immédiate des résistances pulmonaires et déclenche la fermeture des shunts en commençant par la valvule du foramen ovale puis en continuant, en quelques jours, par le canal artériel.

Des exemples et observations physiopathologiques

L'influence de la pompe respiratoire sur l'hémodynamique est observée par la chute post-natale immédiate des résistances vasculaires pulmonaires [22].

Ceci est déclenché par les mouvements respiratoires, en créant des forces des cisaillements sur les parois endothéliales pulmonaires avec une pression différentielle intérieure indirecte plus proche de la loi de Newton.

Ce qu'explique l'échec des anastomoses bicavo-pulmonaire chez les nourrissons de moins de 2 ans se rapporte à l'incapacité de la pompe respiratoire, en raison du développement insuffisant des muscles de la cage thoracique, d'assurer par des forces de cisaillement suffisantes le drainage veineux nécessaire [23,24].

Le drainage veineux est ainsi directement conditionné par ces forces, qui assurent son retour vers les cavités atrio-ventriculaires droites au moment du remplissage diastolique.

Un bon remplissage du cœur droit (ou précharge), est capital pour un fonctionnement harmonieux de tout le système circulatoire.

L'augmentation de la précharge améliore la force contractile du VD qui va améliorer les forces de cisaillement (shear stress) apparaissant dans la circulation pulmonaire.

Celles-ci vont provoquer une baisse des résistances vasculaires en raison de l'excrétion du monoxyde d'azote (NO) qu'elles induisent dans l'endothélium pulmonaire et cette baisse des résistances pulmonaires (ou post charge) va améliorer à son tour le débit cardiaque global.

Ceci explique pourquoi les dérivés nitrés si efficaces dans le traitement de l'infarctus du myocarde en cas d'atteinte du ventricule gauche, peuvent au contraire en cas d'ischémie du ventricule droit, risquer d'entraîner le décès du sujet puisque le remplissage de ce ventricule diminuerait en cas d'administration du fait même de l'action vasodilatatrice des nitrites.

Autre exemple évocateur, la position acrobatique assise prise spontanément par un enfant atteint d'une tétralogie de Fallot. Pendant la crise, en raison de l'augmentation des résistances pulmonaires, l'enfant devient bleu. En prenant cette position assise, l'enfant bleu augmente artificiellement les résistances vasculaires du côté gauche ce qui aura pour effet de détourner un plus grand volume pulsatile dans le circuit artériel pulmonaire à travers la communication inter ventriculaire (CIV), positionnée à cheval de deux gros vaisseaux (aorte et artère pulmonaire). Ainsi ce phénomène, amélioration hémodynamique avec la baisse des résistances pulmonaires, qui pourraient être induite par une injection d'adrénaline aussi bien pendant une crise de Tétralogie de Fallot (TOF).

Les forces de cisaillement ainsi augmentées vont forcer l'endothélium pulmonaire à produire plus de NO (monoxyde d'azote) ce qui augmentera immédiatement le flux et le rythme dans l'arbre artériel pulmonaire, de façon proche de la loi de Bernoulli.

Hémodynamique du cœur droit

En règle générale toute augmentation des résistances dans un circuit hydraulique entraîne un dysfonctionnement de la pompe d'injection. C'est ce qui explique que l'augmentation des résistances vasculaires (postcharge) du côté gauche entraîne un dysfonctionnement du ventricule gauche dont l'amélioration ne pourra provenir que de la baisse de cette postcharge (action vasodilatatrice des nitrites en cas d'infarctus gauche).

En pratique les perturbations des forces circulatoires accessoires peuvent entraîner un dysfonctionnement endothélial et des troubles hémodynamiques. Citons quelques exemples, selon notre classification précédente, afin de comprendre le phénomène :

En **Zone 1**, fortement dépendante de ces forces accessoires, on peut constater que les altérations de celles-ci provoquent des troubles cardiovasculaires et circulatoires presque identiques chez les astronautes et chez les plongeurs professionnels. Malgré la grande différence de pression constatée dans ces deux cas (absente chez les astronautes, très forte chez les plongeurs) les troubles observés sont liés à la défaillance de la pompe de drainage veineux (capacitance veineuse élevée par un manque de la gravité dans l'espace, et par écrasement dans l'eau).

Il en est de même pour le développement précoce des rides chez les plongeurs, et l'œdème facial sévère en haute altitude [25].

En dehors de ces conditions extrêmes, l'œdème du visage autour des yeux (paupières gonflées) se manifeste plus le matin après une longue nuit de sommeil, (avec parfois des maux de tête) pour disparaître progressivement avec la reprise des activités.

Cette congestion lymphatique démontre l'effet de la diminution de la gravité sur le retour veineux de la face, entraînant une accumulation de produits toxiques (syndrome inflammatoire, radicaux libres, ralentissement de la circulation caverneuse).

Chez l'enfant, pourtant, malgré une vascularisation et une surface de la face plus importantes que chez l'adulte, l'effet de la gravité pendant les longues périodes de sommeil reste minime.

La formule de Parkland connue sous le nom de « loi de 9's » appliquée chez les grands brûlés prouve l'importance de la surface corporelle de la tête comparé au reste du corps (18%) chez les enfants contre (9%) adultes [26].

Un bon sommeil en effet favorise l'anabolisme (réparation et régénération) du processus angiogénèse - apoptose interdépendance qui dépend des forces de cisaillement complétées par un bon drainage veineux. Or, l'enfant ou le nouveau-né ont un rythme cardiaque très élevé parfois double de celui de l'adulte (même pendant le sommeil).

Ces forces de cisaillement sont donc primordiales pour permettre l'accélération naturelle de la croissance. Avec un tel flux, un tel rythme et une telle surface faciale l'enfant garde toujours un visage lisse, sans le moindre signe de tuméfaction, avec une peau satinée même après de très longues périodes de décubitus dorsal.

La différence morphologique entre adulte et enfant joue donc un rôle important dans l'explication de ce phénomène.

De plus, afin d'assurer un bon drainage veineux évitant les effets secondaires causés par la gravité pendant le sommeil, deux autres éléments viennent compléter l'action des forces accessoires de la circulation :

- les cris qui représentent un formidable exercice de pompe musculaire au niveau du visage empêchant la stase veineuse.
- un cou quasi absent (web neck) rendant le drainage veineux encore plus dépendant de la pompe respiratoire.

Les effets hémodynamiques dans les autres zones, **Zone 2** à **Zone 4**, sont également troublés par une diminution des retours veineux en **Zone 1**. Les effets cardio-pathogéniques directs (ischémie du myocarde ou malformation cardiaque) peuvent donc provoquer des troubles hémodynamiques majeurs.

Maintenir en Zone 5, qui est une zone clé, une bonne hémodynamique est la condition d'un bon fonctionnement global du système circulatoire. Des résistances élevées en **Zone 5** (postcharge), peuvent provoquer des troubles hémodynamiques rétrogrades avec une dépression hémodynamique systémique. Les syndromes d'hypertension pulmonaire aigue ou chronique dépendent du niveau d'excrétion du monoxyde d'azote et du remodelage vasculaire, autrement dit des forces de cisaillement.

Le cœur droit dans la crise de Fallot sollicite donc paradoxalement l'augmentation de la postcharge à gauche pour faire baisser la sienne ! Cela signifie qu'il n'hésite pas à mettre provisoirement en péril le cœur gauche pour améliorer son propre hémodynamique et ensuite seulement améliorer à nouveau celle du cœur gauche (Tableau 1).

Tableau 1 : Domination du Cœur droit sur le Cœur gauche à travers les résistances pulmonaires :

	Cœur Droit	**Cœur Gauche**
Résistances Systémiques Basses	*Mauvaise* hémodynamique [1]	*Bonne* hémodynamique
Résistances Systémiques Élevées	*Bonne* hémodynamique [2]	*Mauvaise* hémodynamique
Résistances Pulmonaires Basses	*Bonne* hémodynamique	*Bonne* hémodynamique
Résistances Pulmonaires Élevées	*Mauvaise* hémodynamique	*Mauvaise* hémodynamique

1= Nitrites et Infarctus du Ventricule droit. 2 = Crise de Fallot.

À l'heure actuelle, en cas de défaillance du ventricule droit, le schéma thérapeutique habituel consiste à :

a) augmenter le volume sanguin par des perfusions intraveineuses.

b) augmenter la fréquence cardiaque (atrial kick), par des chronotropes ou par un pacemaker (entraînement électrique).

C'est dans les deux cas une augmentation des forces de cisaillement (volume et rythme) obtenue par des méthodes non physiologiques et non dénuées d'effets secondaires.

Force de Cisaillement → Fonction - Dysfonctionnement Endothélial :

Le flux et rythme sont les deux piliers principaux qui influencent l'effet de la force des cisaillements sur la fonction endothéliale de la vie anténatal.
Une perturbation des ces deux facteurs (flux et rythme) peuvent entrainer des pathologies cardiovasculaires quelque soit congénitales ou acquises.

Les méthodes des investigations actuelles utilisées en cardiologie sont plus ou moins que des détecteurs du flux et du rythme autrement dit hémodynamique (ex : les stéthoscopes, écho, IRM, etc.).

En règle générale toutes stratégies thérapeutiques cardiovasculaires se concentrent sur le maintien du flux et du rythme circulatoire soit des ralentisseurs (ex : les β-bloquants), des accélérateurs du rythme (ex : les catécholamines), vasodilatateurs ou vasoconstricteurs, les interventions chirurgicales, la cardiologie interventionnelle.

Une réparation valvulaire ou une reconstruction ventriculaire ne représente qu'une reconstruction d'un volume du flux sanguin qui doit être éjecté par une cavité ventriculaire à travers une surface valvulaire au fur et à mesure aux besoins physiopathologiques de l'individu.

Les forces des cisaillements peuvent être directe (intravasculaire) ou indirecte (extravasculaire). Par exemple toute stimulation externe de la fonction endothéliale accélère l'angiogénèse donc ici, la croissance tumorale.

Parfois une membrane externe qui empêche les réponses aux pressions selon la loi de Laplace, peut isoler l'effet stimulant de ces forces externes sur les organes en question. De même, une différence entre les tumeurs malignes et les tumeurs bénignes pourrait provenir de la présence ou non d'une capsule qui joue un rôle protecteur contre la propagation des ondes pulsatiles provenant des organes voisins. Ceci peut expliquer le pronostic plus péjoratif des cancers des organes mobiles (estomac, poumons) ainsi que des tumeurs d'organes richement vascularisés comme le cerveau, comparé à celui des cancers d'organes plus fixes comme la thyroïde ou la prostate. D'après ce concept, l'isolement d'une tumeur par une capsule artificielle augmentera l'efficacité thérapeutique en cancérologie.

Autre exemple cité auparavant sur les malformations congénitales sont le plus souvent associées à une diminution pendant les premiers mois de la grossesse, du liquide amniotique qui isole le fœtus des ondes pulsatiles propagées par les organes maternels voisins.

Pareillement les grandes veines comme les veines caves, jugulaires internes qui gardent toujours un remodelage bas, sont enveloppées dans une membrane externe (sheath), afin de se protéger des forces de cisaillement propagées des artères voisines (aortes, carotides,).

Toute intervention perturbant la stimulation endothéliale par la force de cisaillement, telle que, par exemple, une pathologie ou une opération chirurgicale, entraîne un dysfonctionnement endothélial avec des conséquences pouvant être dramatiques [27-29].

En cas de troubles de l'interdépendance angiogenèse–apoptose, des conditions pathologiques se produisent favorisant la malignité, le psoriasis, les anomalies congénitales, les cardiopathies ischémiques, etc. Un exemple classique de déséquilibre angiogenèse–apoptose, est l'insuffisance cardiaque due à une destruction progressive des cardiomyocytes par l'apoptose, généralement suivie par un mécanisme de compensation angiogénique se traduisant par une hypertrophie ou une dilatation du myocarde [30].

Autre exemple dans la vie anténatale, le développement du fœtus est plus affecté par les forces hémorhéologiques qui conditionnent le sens du flux sanguin, plutôt que par la fonction de la pompe cardiaque elle-même. Ceci explique la survie d'un fœtus atteint d'anomalies cardiaques incompatibles avec la vie, comme l'hypoplasie du cœur gauche, qui continue son développement normalement sans que la grossesse soit interrompue.

Au contraire, les situations qui provoquent un véritable danger pour la vie du fœtus, sont celles qui affectent les forces hémorhéologiques telles que l'arythmie fœtale ou le syndrome pré-éclampsie maternel.

Les applications thérapeutiques de l'angiogenèse dans la pathologie cardio-vasculaire sont principalement axées sur deux mécanismes permettant de réaliser le remplacement des tissus apoptotiques et d'assurer leur vascularisation déjà compromise, qui sont : néovascularisation et cardiogénèse.

En pédiatrie le processus cardiogénique est parfois différent de celui des adultes : chez ceux-ci, on est confronté à des lésions ischémiques nécessitant la restauration de la zone infarcie. En pédiatrie c'est le plus souvent une augmentation de la masse ventriculaire gauche qui est recherchée.

Habituellement la revascularisation peut être obtenue directement via les interventions chirurgicales ou de cardiologie interventionnelles. Sinon, avec un lit vasculaire très malade ces méthodes directes deviennent incertaines, nécessitant le développement de méthodes alternatives qui ont prouvé leur efficacité dans l'amélioration de l'angiogenèse.

Ce sont en particulier l'apport du grand épiploon pour rétablir la vascularisation ainsi que le sauvetage des organes ischémiques, les abrasions épicardiques, l'insertion directe de l'artère mammaire interne par Vinberg ou la revascularisation laser transmyocardique en percutané. Toutes ces méthodes sont des procédures angiogéniques avec des rendements variables mais prouvés.

Les applications thérapeutiques des dispositifs d'assistance circulatoire pulsatiles, comme la contre pulsion externe renforcée (EECP), l'assistance ventriculaire gauche (LVAD), la transplantation cardiaque hétérotopique, la cardio et aorto-myoplastie, ont prouvé l'efficacité de la force de cisaillement laminaire (LSS) pour induire l'angiogénèse.

Il est intéressant de noter que tous ces dispositifs stimulent la membrane des cellules endothéliales, produisant l'angiogénèse, indépendamment de leur mécanisme, qu'il soit direct ou indirect, intra ou extra-luminal, et le type de tissu endothélial concerné : veineux, artériel ou endocarde.

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Chapitre III

Stratégie thérapeutique - Objectifs – Facteurs physiopathologiques

STRATEGIES THERAPEUTIQUES

Afin d'obtenir une fonction thérapeutique plus optimale de la fonction endothéliale stimulée par la force de cisaillement, nous définissons notre stratégie thérapeutique au fur et à mesure des objectifs souhaités et facteurs physiopathologiques du système circulatoire.

Objectifs

Nous visons en particulier, deux objectifs principaux :

- À court terme : une amélioration de l'hémodynamique et de la microcirculation. Celle-ci est le plus souvent représentée en situation de urgence devant un tableau du choc hémodynamique. Nos études animales présentées dans cette thèse se focalisent sur cet objectif en prouvant la crédibilité et l'efficacité des nos nouveaux dispositifs d'assistance circulatoires en urgences.
- À long terme : restauration et préservation de la fonction endothéliale. Ce qui nécessite la préparation des modèles du dysfonctionnement endothélial chronique. Celle-ci est prévue dans nos prochaines études.

Facteurs physiopathologiques du système circulatoire

Nous approchons le système circulatoire de façon plus radicale par rapport aux rôles physiopathologiques et besoins hémodynamiques avec des nouveaux dispositifs d'assistance circulatoires.

- ***Rôle et approche thérapeutique du cœur***

Selon Anderson, un des pionniers et fondateurs de l'assistance cardiaque mécanique, dont le cœur extracorporel, la fonction cardiaque se résume en quatre points essentiels [1]:

1) Le cœur est une pompe du remplissage passif.
2) Les oreillettes augment le débit cardiaque en provoquant un flux continu veineux vers les ventricules par des contractions intermittentes, et non par le pompage des ventricules.
3) La vitesse de la circulation est normalement déterminée par les facteurs extracardiaques.

4) C'est seulement au cours de l'insuffisance cardiaque que le cœur est le régulateur du débit cardiaque.

Les objectifs thérapeutiques de l'insuffisance cardiaque d'après Anderson poursuivent quatre buts :

1) Avoir une contractilité cardiaque plus forte et plus rapide.
2) Diminuer la résistance à l'éjection du sang des ventricules (la postcharge).
3) Abaisser la pression cardiovasculaire moyenne par les diurétiques et la restriction de sel et d'eau.
4) Restaurer l'action auriculaire si elle est compromise par la fibrillation auriculaire ou un rythme nodal.

Or, des études récentes ont démontré des changements dans l'expression de l'acide micro ribonucléique (miARN) dans l'insuffisance cardiaque, qui ont également été observés après décharge du ventricule par assistance mécanique [2]. Ce rôle pathophysiologique joué par miARN dans les processus de la défaillance cardiaque, peut être lié à un ensemble de mécanismes en aval (dans la circulation), sur lesquels il est possible d'agir pour inverser des phénotypes pathologiques [3]. En substance, ils peuvent fournir des cibles potentielles de traitement pour retarder ou inverser le remodelage cardiaque ou la fibrose [4].

Récemment la découverte de cellules progénitrices endothéliales (CPE) dans la circulation, a révolutionnée le domaine de la recherche sur l'angiogénèse [5]. Des études cliniques ont été lancées pour déterminer le potentiel de ces cellules pour stimuler la réparation des tissus après une lésion ischémique. On fait l'hypothèse que les cellules progénitrices endothéliales (CPE) provenant de moelle osseuse ont un rôle dans la réparation de la dysfonction endothéliale et de la progression de la maladie cardio-vasculaire [6-8].

Les données sur le miARN et les CPE sont cohérentes à notre stratégie thérapeutique dans la défaillance cardiaque, qui est focalisée sur le circuit plutôt que le cœur. La mobilisation des colonnes de sang dans les circuits *systémique*, *pulmonaire* et *capillaire, effectuée par nos dispositifs pulsatiles,* peut créer une stimulation de la fonction endothéliale plus physiologique et sans aucune intervention directe ni stimulation de la pompe cardiaque.

Par rapport aux concepts actuels cette nouvelle pensée endothéliale, s'appuie sur des nombreux principes observés dans notre étude comme :

- Le cœur représente une force motrice circulatoire, parmi plusieurs autres aussi importantes.
- Le cœur est issu de l'endothélium, qui est le précurseur du système circulatoire.
- Presque tous les traitements proposés actuellement en cas de défaillance cardiaque, sont des produits exogènes chimiques, qui simulent une fonction endothéliale saine.
- Les assistances cardiaques mécaniques utilisées de nos jours, imitent la pompe cardiaque qui est une pompe de type III, passive par une pompe de type I (péristaltique) ou de type II (centrifuge) [1].
- Une défaillance cardiaque est un dysfonctionnement endothélial, qui devrait être traité à l'origine, par le biais de l'endothélium qui dépend de la force de cisaillement [9].

Afin de réparer et restaurer la fonction cardiaque, nous nous sommes concentrés sur la stimulation de la partie endothéliale du cœur : l'endocarde et l'endothélium vasculaire.

L'endothélium vasculaire contrôle directement la fonction des artères coronaires, et indirectement la fonction cardiaque par le contrôle de l'approvisionnement sanguin coronaire du myocarde. Par ailleurs, l'endothélium cardiaque dans les capillaires du myocarde et de l'endocarde sont adjacentes aux cardiomyocytes, ce qui permet une communication cellulaire directe par des signaux entre les différents types de cellules [10,11].

Le traitement de la défaillance cardiaque par le maintien des forces de cisaillement a été validé par la transplantation cardiaque hétérotopique et l'EECP qui ont démontré la restauration du muscle cardiaque originel. Ceci passe par des processus liés à fonction endothéliale tels que cardiogénèse, angiogénèse.

En revanche, les essais de réparation du myocarde par les méthodes actuelles (thérapies cellulaires) sont en plein progrès. Néanmoins, ces méthodes de la thérapie cellulaire sont confrontées aux différentes propriétés biophysiques et physiopathologiques de l'endocarde.

L'endocarde qui fait partie des tissus endothéliaux, peut être distingué en 4 zones différentes:

I. *L'endocarde auriculaire,* surtout au niveau de l'oreillette droite qui joue un rôle hémodynamique important, dont le contrôle du rythme cardiaque [12], la morphogénèse cardiaque [13], ainsi qu'une fonction endocrine [14]. Les troubles de la force de cisaillement dans cette zone peuvent provoquer des arythmies (par exemple une augmentation de la pression atriale après un Fontan), [15], ou une perturbation hormonale (sécrétion de peptides natriurétiques) [16]. *Dans cette zone et en cas d'assistance cardio-circulatoire, nous devons impérativement maintenir une pression veineuse basse (< 15 mmHg).*

II. *L'endocarde du ventricule gauche (VG) :* l'endocarde dans cette zone, dépend directement de la circulation coronaire principale et du remplissage des artères coronaires pendant la diastole. La force de cisaillement produite avec une pression différentielle (systolique et diastolique), joue un rôle majeur dans la régularisation de la fonction cardiaque dans cette zone. Des exemples pathologiques de la perturbation de la force des cisaillements au niveau de l'endocarde myocardique gauche sont la sténose aortique serrée [17], l'incompétence mitrale ischémique due à des anomalies coronaires (artère coronaire gauche naissant de l'artère pulmonaire) qui provoque des lésions de fibroélastose endocardique et un dysfonctionnement du pilier antérieur [18]. *Afin de restaurer la fonction cardiaque par le biais de l'endocarde du VG, il faut impérativement éviter une pression diastolique élevée par : a) décharger le VG ; b) réduire la postcharge par une perfusion artérielle pulsatile ; c) éliminer chirurgicalement les causes mécaniques (sténose aortique, dysfonctionnement papillaire mitral, etc).*

III. L'endocarde du ventricule droit (VD) : l'hémodynamique du VD, comme nous l'avons détaillé auparavant (chapitre II), est dépendant de la postcharge pulmonaire [19], et l'augmenation de la précharge surtout en Zone 2 [20]. *Une stimulation de l'endocarde du VD par une assistance cardio-circulatoire, devrait respecter les objectifs principaux : a) une baisse de la postacharge pulmonaire ; b) maintenir un bon remplissage (précharge) du VD ; c) préserver le remodelage physiologique du cœur droit.* Malheureusement, ceci n'est guère respecté avec les assistances cardiaques actuelles qui déchargent le VD.

IV. L'endocarde au niveau du septum inter-ventriculaire : La présence du système de conduction et le remodelage spécifique dans cette zone, pose des problèmes hémodynamiques majeurs comme les arythmies ventriculaires, [21-23], ou la rupture du septum [24]. Ceci rend plus difficile le remplacement et la restauration (angiogénèse-cardiogénèse) des zones infarcies par des stimulations endothéliales exogènes [25].

- ***Rôle et approche thérapeutique du cycle cardiaque***

Le cycle cardiaque (Figure 2) se compose de deux phases systolique et diastolique, conséquence des activités électriques et mécaniques du cœur.

L'activité électrique de la systole auriculaire, qui représente 30% du débit cardiaque, commence par le début de l'onde P sur l'ECG due à la dépolarisation de membrane au niveau du nœud sinusal, puis se propage vers le nœud atrio-ventriculaire, le faisceau du Hiss et les fibres de Purkinje.

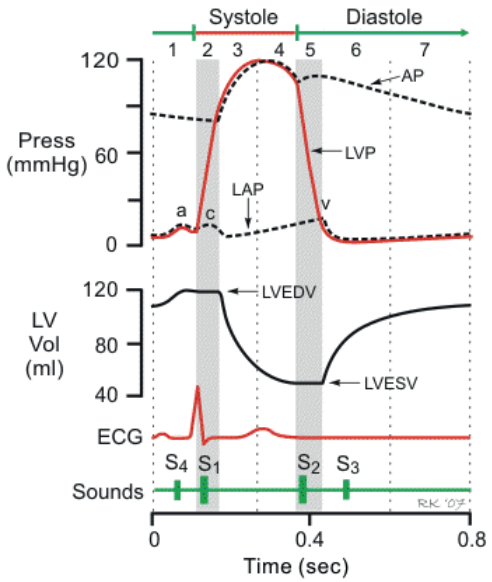

Figure 2 : Cycle cardiaque (Klabunde RE)

La systole ventriculaire qui se caractérise par les ondes « QRS » sur l'ECG se divise en trois phases : a) phase de contraction isovolumétrique; b) phase d'éjection rapide; c) phase d'éjection lente.

L'activité électrique du cycle cardiaque présentée par la contractilité cardiaque qui se déclenche une dépolarisation cellulaire par un stimulus électrique externe (une cellule adjacente), ou spontanément par certaines cellules « pacemaker » qui se trouvent dans le nœud sinusal, et le nœud septal. L'action potentielle de membrane par la dépolarisation non spontanée des cellules (comme les myocytes auriculaires, myocytes ventriculaires et des cellules de Purkinje) est de caractères très rapides. En revanche l'activité des cellules pacemaker est produite par des cellules ganglionnaires avec un taux des activités peut être modifiée de manière significative par des facteurs externes tels que par les nerfs autonomes, hormones, médicaments, ions, et de l'ischémie / l'hypoxie.

En principe l'action potentielle de membrane cellulaire se déterminent par la concentration des ions à l'intérieur (K^+) et à l'extérieur de la cellule (Na^+ ; Ca^{++}), la perméabilité de canaux ioniques spécifiques ; et l'activité des pompes électrogènes (Na^+ / K^+ - ATPase et Ca $^{++}$ pompes) qui maintiennent les concentrations d'ions à travers la membrane.

Le potentiel d'action cardiaque *se divise en 5 phases (Figure 3):*

Phase 4 : représente le potentiel de membrane au repos pendant la diastole, jusqu'à ce qu'elle est stimulé.

Phase 0 est la phase de dépolarisation rapide. La pente de la phase 0 représente le taux maximum de dépolarisation de la cellule. Cette phase est due à l'ouverture rapide des canaux Na + causant une augmentation rapide de la conductivité de la membrane de Na^+.

Phase 1 durant laquelle le potentiel d'action cardiaque se produit par l'inactivation des entrées rapides de Na^+ et la circulation des ions K^+ et Cl^- vers l'extérieur.

Phase 2 présente un « plateau » avec un potentiel d'action maintenu par un équilibre entre le mouvement vers l'intérieur de Ca^{2+} par le biais de canaux calciques de type l et le mouvement vers l'extérieur de K^+ à travers des canaux lents de potassium (échangeur sodium-calcium), et la pompe de sodium/potassium.

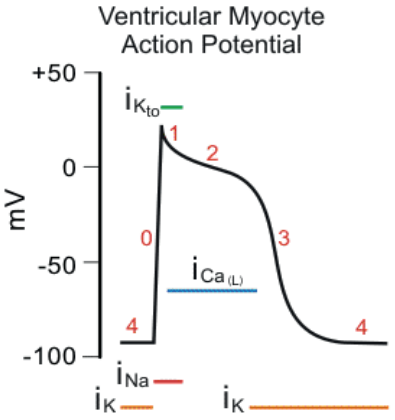

Figure 3: Les 5 Phases d'action potentielle cardiaque (Klabunde RE)

Phase 3 la phase « repolarisation rapide » du potentiel d'action.

L'activité mécanique du cycle cardiaque représentée par le volume et la pression du flux sanguin veineux et artérielle pompés par le cœur :

En générale les deux oreillettes maintient un flux veineux continu et les deux ventricules pompent le sang en série avec un débit cardiaque intermittent, dans deux lits vasculaires interposés (systémique et pulmonaire respectivement) [1].

Celle-ci est aidée en effet, par des nombreux facteurs :

I. Morphologiques :
   a) Auriculaire dont : i) l'absence de valves d'entrée qui pourra interrompre le flux sanguin pendant la systole auriculaire; ii) des contractions auriculaires systoliques incomplètes ; iii) des contractions auriculaires douces;

iv) le «lâcher prise» de l'oreillette qui doit être programmé de manière qu'ils se détendre avant le début de la contraction ventriculaire, pour être en mesure d'accepter flux veineux sans interruption [1].

b) Ventriculaire comme nous l'avons précédemment détaillé en (chapitre I), sur la différence morphologique entre VD et VG.

II. Le rythme cardiaque qui est réciproque du volume d'éjection systolique, par exemple une diminution de la fréquence cardiaque peut augmenter le volume d'éjection systolique; tout en augmentant la fréquence cardiaque pourra diminuer le volume d'éjection systolique.

III. Les réserves et les dépenses énergétiques du cœur qui ont nécessaires pour maintenir un débit imposé par les régulateurs périphériques vasculaires.

IV. Des effets périphériques-vasculaires, plutôt que par des variables cardiaques :

a) Une pression cardiovasculaire moyenne positive, qui existe indépendamment de l'action de pompage du cœur [1].

b) Le retour veineux car le cœur s'adapte à la précharge en changeant sa force de contractilité. L'étirement accrue des myocytes ventricules pendant la diastole produit à la vigueur une augmentation de la contraction à la systole (loi de Starling du cœur).

c) Les facteurs neuro-humoraux qui augmentent la pression cardiovasculaire moyenne, ils peuvent aussi augmenter le rythme et la contractilité ventriculaire [26].

d) Les barorécepteurs chimiques (dans la racine aortique) et neurologiques (la bulbe carotide) [27,28].

e) Les forces motrices circulatoires accessoires [29].

Nous admettons que le rythme cardiaque déclenché par le biais de plusieurs mécanismes (spontané, canaux des ions, neurologiques, etc.) permet la circulation du sang et maintient une fonction endothéliale par la force de cisaillement.

En revanche, en cas de défaillance cardiaque, nous imposons la fréquence des pulsations par nos dispositifs d'assistance circulatoire, indépendamment du rythme cardiaque.

La force de cisaillement engendrée par ces nouveaux dispositifs pulsatiles, permettra l'augmentation de la précharge et la baisse de la postcharge par le biais des plusieurs médiateurs vasodilatateurs, secrétés par l'endothélium.

La synchronisation des ces dispositifs pulsatiles par rapport au cycle cardiaque, sera effectuée selon les types de dysfonctionnement endothélial.

- ***Rôle et approche thérapeutique du dysfonctionnement endothélial***

La perturbation de la fonction endothéliale est le facteur principal des troubles hémodynamiques et circulatoires, dans toutes presentations cliniques [30]: malformations congénitales [31], choc hémodynamique, syndrome de défaillance multiviscérale [32].

Dans cette nouvelle stratégie thérapeutique, nous divisons les patients atteints de dysfonctionnement endothélial en trois catégories comme suivants:

- **Type (A) :** représente les patients atteints de dysfonctionnement endothélial manifesté par une défaillance cardiaque.
- **Type (B) :** représente les patients atteints de dysfonctionnement endothélial avec une bonne fonction cardiaque comme : l'hypertension artérielle (systémique ou pulmonaire), dysfonction érectile (syndrome X), les diabètes, maladies neurodégénératives (d'origine ischémique), stroke, ostéoporose, syndrome de vieillissement précoce, … etc.
- **Type (C) :** représente des sujets sains, prédisposés au développement de dysfonctionnement endothélial comme : le syndrome thromboembolique présenté après une immobilisation de longue durée (voyageurs, fractures) ; les escarres (personnes âgées, les tétraplégiques); des troubles du rythme (astronautes) ; l'ostéoporose (plongeurs professionnels) ; le syndrome inflammatoire (exposition solaire), fatigue (athlètes soumis à des exercices physiques excessifs) … .

La synchronisation de la pulsation avec le rythme cardiaque et surtout la phase diastolique du cœur est strictement guidée par les indications thérapeutiques selon ces 3 catégories du dysfonctionnement endothélial.

Dans les patients du Type A, les appareils d'assistance cardiaques doivent être impérativement désynchronisés du rythme cardiaque. Pourtant cette synchronisation est recommandée avec les patients en catégorie B. En revanche avec la catégorie C, l*a synchronisation des dispositifs est relative, car le débit cardiaque s'adapte aux retour veineux selon la loi de Starling* [33].

- ***Rôle et approche thérapeutique de la microcirculation*** *:*

Le maintien du bon fonctionnement des organes par le biais de la microcirculation générale des organes constitue un effet caractéristique de notre concept thérapeutique.

Comme on le sait, l'être humain est un organisme multicellulaire dont la biologie cellulaire joue un rôle principal en matière de développement, l'entretien, le bon fonctionnement des organes vitaux (homéostasie).

Normalement la microcirculation dépend directement de nombreux médiateurs vasodilatateurs sécrétés par l'endothélium, tels que le monoxyde d'azote (NO), la prostacycline, les inhibiteurs de la phosphodiestérase 5 [34,35].

Le flux sanguin pulsatile artériel se traduit par la distribution à peu près égale de sang à tous les tissus de l'organisme. Ce phénomène ne se produirait pas avec un flux non pulsatile, constant [1].

Théoriquement, les forces tangentielles de cisaillement qui stimulent la fonction endothéliale de la microcirculation, pourraient être réalisées de deux manières :

I. En fonction de la 2ème loi de Newton : la force de cisaillements est induite par une pression différentielle (pulse pressure) plutôt que par la fréquence de cisaillement.
II. En fonction de la 3ème formule de Bernoulli : les forces de cisaillement sont liées au frottement au niveau des parois intérieures, plutôt qu'à la pression différentielle.

Dans des conditions hémorhéologiques normales, le comportement hémodynamique de la microcirculation est proche de celui de la loi de Newton. Un exemple symbolique est observé chez les athlètes de haut niveau : une bonne performance physique est obtenue avec un rythme cardiaque lent mais avec une augmentation du volume d'éjection systolique (stroke volume ou pression différentielle). En revanche, dans les états hémorhéologiques anormaux, la microcirculation présente un comportement qui s'apparente à celle de la loi de Bernoulli, tel qu'il est interprété par l'effet Fahraeus-Lindqvist dans lequel les couches du plasma sont freinés contre les parois vasculaires, contrairement aux érythrocytes qui bougent plus vite au centre du vaisseau. Cela pourrait expliquer l'absence de cyanose chez les patients anémiques atteints d'un taux d'hématocrite bas, contrairement à ceux des patients avec des hématocrites élevés, plus souvent présentés par une cyanose avec doigts en baguettes de tambour (clubbing fingers)

causée par les agrégations des érythrocytes dans la microcirculation digitale [36].

- ***Rôle et approche thérapeutiques des lois de physiques:***

L'application clinique de la force des cisaillements par des nouveaux dispositifs d'assistance circulatoire, devrait être effectuer selon les critères biophysiques et physiopathologiques du système circulatoire, tout en respectant leurs adaptations par apport aux lois de la mécanique des fluides, comme suit :

1. *Sur le circuit du cœur gauche*, la stimulation endothéliale par la force de cisaillement doit être induite selon les principes de Newton, en livrant un volume du flux pulsatile avec une pression différentielle (pulse pressure), quasi constant dans le circuit artériel systémique.
2. *Sur le circuit du cœur droit*, en plus des lois physiques de Newton et de Bernoulli, l'effet de la gravité (loi de Pascal) devrait être considéré afin de produire une stimulation endothéliale optimale par la force de cisaillement. Comme nous avons souligné précédemment, sur la biophysique du circuit cœur droit, l'artère pulmonaire (AP) se caractérise par un niveau de remodelage faible (Z5), similaire aux veines systémiques (Z1), et toutefois, avec une compliance qui est beaucoup plus importante que celle des grosses veines [37]. Normalement, la compliance de l'arbre artérielle pulmonaire et la stimulation endothéliale, par la force des cisaillements induits par la pompe respiratoire sont des protecteurs naturels contre l'athérosclérose pulmonaire. En revanche, il faut impérativement éviter toute perturbation du remodelage physiologique du cœur droit (influencé par loi de Laplace). Ce qui signifie, toute perfusion directe intravasculaire (veines systémiques et artère pulmonaire) avec un flux pulsatile en fonction de la loi de Newton (pression différentielle) doit être évitée car elle pourrait induire de graves troubles hémodynamiques tels que : a) le remodelage pulmonaire irréversible comme le syndrome d'Eisenmenger [38]; b) la maladie des greffons veineux après un pontage coronarien [39]. Ceci pourrait expliquer l'échec des dispositifs d'assistance circulatoires pulsatiles actuels, utilisés en cas de défaillance ventriculaire droite [40].

- ***Rôle et approche thérapeutique du réservoir naturel du cœur droit***

Actuellement, on observe un taux de morbidité et mortalité très élevés chez les patients atteints d'insuffisance cardiaque droite [41].

Nous considérons le cœur droit comme un outil physiologique pour traiter presque tous les genres de troubles hémodynamiques et circulatoires, chez les adultes comme en pédiatrie. Le circuit du cœur droit contient > 64% du volume sanguin contenu par une masse importante de cellules endothéliales. Ce stock naturel de volume sanguin et cette masse endothéliale pourrait être stimulés par un bon dispositif pulsatile, adaptable aux critères biophysiques, physiopathologiques et morphologiques des différentes zones du circuit du cœur droit.

- ***Rôle et approche thérapeutique de la postcharge pulmonaire***

La réduction des résistances vasculaires pulmonaires est la clé de l'amélioration hémodynamique immédiate. Elle pourrait être réalisée par l'augmentation des effets physiologiques de la force de cisaillement sur la masse endothéliale du circuit droit directement sur la masse endothéliale en zone 5 (artère pulmonaire), ou/et indirectement sur la masse endothéliale en zone 1.

- ***Rôle et approche thérapeutique du modèle animal***

Le choix du modèle animal est indispensable pour les évaluations des nouveaux procédés thérapeutiques avant de passer à l'étape clinique. Quelles que soient les méthodes actuellement appliquées, il reste toujours un chois difficile et souvent loin de la réalité cliniques.

Citons quelques exemples sur les inconvénients des modèles appliqués à l'heure actuelle :

- Le modèle du infarctus du myocarde est malheureusement guidé par le coût plutôt que la ressemblance clinique. Par exemple, le rat comme un chois préféré des chercheurs, est loin de la physiologie humaine avec un rythme cardiaque >400 bpm [42]. En plus l'obstruction coronaire qui est souvent pratiquée temporairement (≈ 40 min), par une ligature sur l'IVA est moins précis car prend une large zone du myocarde. Vu la petite taille du cœur, cette ligature prend une partie du VG au même temps avec une partie du septum et VD, ce qui est loin de la réalité fréquentée en clinique. Comme nous avons expliqué dans le texte, les conséquences hémodynamiques et les stratégies thérapeutiques sont complètements différents entre les trois zones (VD, VG et septum) en cas du syndrome ischémique. Un autre modèle comme le chien possède un bon réseau des collatérales ce qui rend l'effet hémodynamique de l'infarctus moins efficace

par apport à l'Homme [43,44]. Le porc comme modèle ischémique est souvent réalisé par une sonde à ballonnet gonflé provisoirement, dans l'IVA est souvent associé avec des traitements préparatoires, hors en réalité clinique, le patient ne se prépare pas avec ce genre des médicaments avant un infarctus aigu [45].

- Le modèle de l'hypertension pulmonaire aigue, aussi souvent réalisé soit par l'hypoxémie, monocrotaline ou un shunt systémique-pulmonare, Néanmoins, un manque du modèle robuste de l'HTAP, est toujours en manque due à diffèrent spectres du tissus pulmonaire entre les espèces et l'être humain [46].
- La défaillance ventriculaire droite aigue, est souvent crée par une embolisation coronaire droite, shunt systémique-pulmonaire, disruption de valvulaire tricuspide [47]. Ces modèles ne représentent pas la forme grave de défaillance du VD qui est souvent présente en postopératoire après une ouverture de chenal VD-AP [48].
- La défaillance cardiaque bi-ventriculaire, souvent réclamé pour la mise à l'épreuve des appareils des assistances cardiaques, qui restent toujours difficile à réaliser chez l'animal. Le plus part de ces dispositifs d'assistance ont été testés en version CAO ou sur un modèle WindKessel qui ont largement loin de l'apsect physiopathologique chez l'Homme [49,50].

Pour le développement de nos nouveaux dispositifs d'assistance circulatoire nous avons choisi un modèle animal pédiatrique proche de la clinique.

Nous avons crée et pour la première fois un tableau du choc cardiogénique chez des porcelets (≈ 10 kg) pour un syndrome ischémique, hypertension artérielle pulmonaire, défaillance ventriculaire droite et biventriculaire aigues. Ceci sera plus détaillé dans la 3ème partie de cette thèse.

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Chapitre IV

- Proposition
- Dispositifs
- Prototypes

Proposition

Le concept actuel propose de restaurer la fonction endothéliale, afin d'améliorer l'hémodynamique des patients, la microcirculation générale des organes vitaux, et rétablir un fonctionnement cardiaque quasi normal.

Ces objectives thérapeutiques doivent être réaliser d'une manière qui est la plus physiologique possible, par l'application des forces tangentielles de cisaillement en utilisant nouveaux dispositifs pulsatiles sans aucune intrusion traumatique, et le moindre invasive que possible.

Le développement d'un dispositif d'assistance circulatoire* optimale, ce qui signifie une amélioration hémodynamique, augmentation de la microcirculation orgue, la restauration et la préservation de la fonction endothéliale chez un patient, devrait compromettre les étapes suivantes : le maintien de la dynamique des écoulements circulatoires dans les circulations systémique et pulmonaire du patient; et temporairement soulager le cœur de sa fonction de pompage.

**Nous employons le terme "dispositif d'assistance circulatoire", au lieu de «dispositif d'assistance cardiaque »*.*

Plus précisément, il y a trois manières de stimuler l'endothélium avec un dispositif d'assistance mécanique comme suit (Figure 5):

1. Stimulation endothéliale interne *directe* qui sera induite par un dispositif du cathéter pulsatile (I).
2. Stimulation endothéliale interne *indirecte* avec un flux de perfusion pulsatile qui sera généré par un dispositif du tuyau pulsatile (II), au niveau du cœur gauche.
3. Stimulation endothéliale externe qui sera induite par un dispositif d'une combinaison pulsatile (III), au niveau du cœur droit, par l'application des pression rythmiques et légères sur les capacitances veineuses et lymphatiques superficielles.

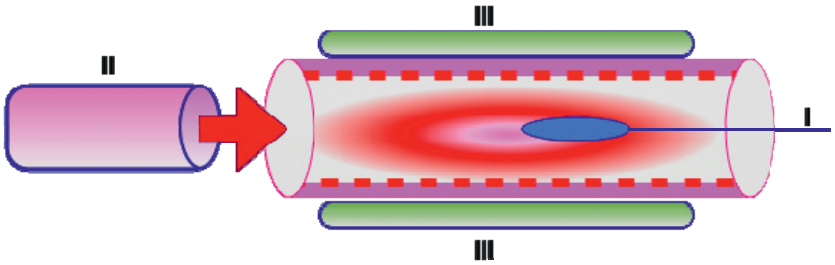

Schéma 6 : Principes des stimulations endothéliale par un dispositif cardiovasculaire pulsatile :

I : stimulation interne directe par un cathéter pulsatile

II : stimulation interne indirecte par un flux pulsatile par le tube pulsatile

III : stimulation externe indirecte par la combinaison pulsatile.

Dispositif

1. Combinaison pulsatile :

Ceci concerne un dispositif d'assistance circulatoire pulsatile non-invasive favorisant la circulation d'un volume sanguin dans le corps d'un sujet, caractérisé en ce qu'il comprend (Schéma 7):

- une structure multicouche flexible destinée à être appliquée sur au moins une partie du corps dudit sujet, cette structure comporte une couche interne flexible du côté du corps et une couche externe plus rigide,
- des moyens de pulsation, reliés à la structure multicouche de sorte que l'ensemble structure + moyens de pulsation est étanche, caractérisé en ce que les moyens de pulsation sont adaptés à créer des pulsations entre les couches internes et externes par l'intermédiaire d'un fluide, dit de pulsation, chacune des pulsations se propageant progressivement dans le sens du retour veineux le long de la partie du corps lorsque la structure est disposée sur le corps.

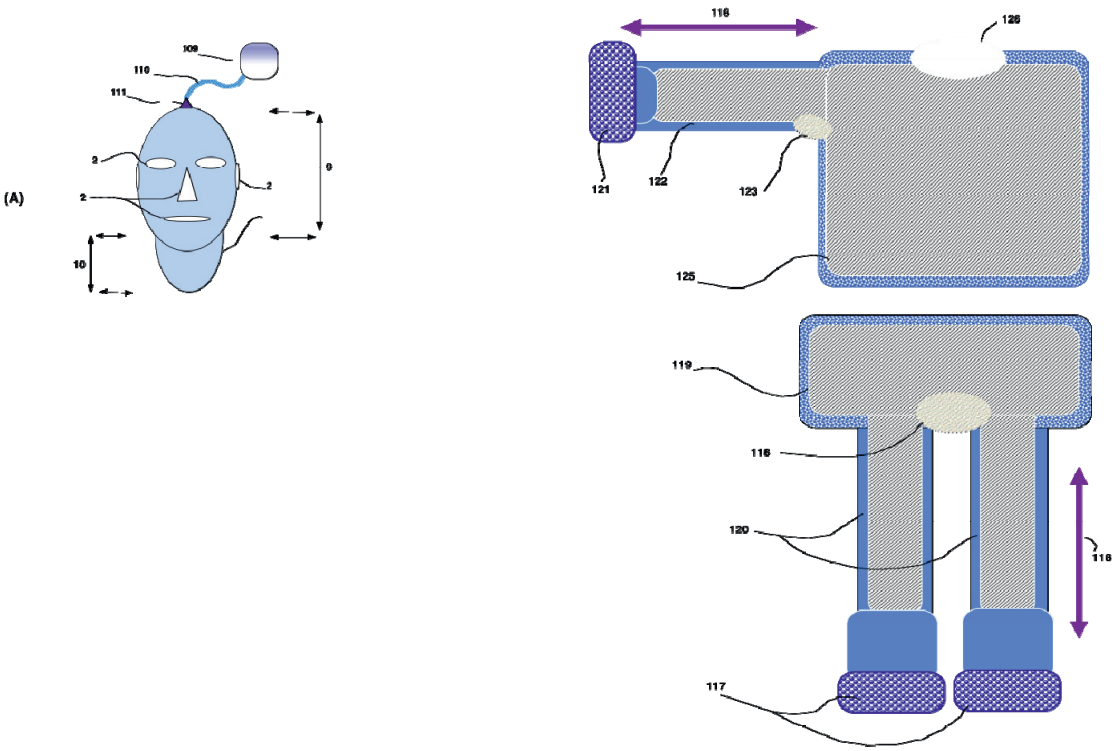

Schéma 7 : Combinaison pulsatile [1,2], composée de veste, de pantalon (droite) et d'une masque (gauche)

2. Tubulure pulsatile:

Dispositif médical pulsatile permettant la circulation d'un flux sanguin caractérisé en ce qu'il comprend (Schéma 8) :

- un tuyau externe (2) présentant une paroi interne (5), une paroi externe (4) et deux extrémités (5), une extrémité destinée à être connectée à une machine de type circulation extracorporelle (CEC) ou à un système d'assistance cardiaque et une extrémité destinée à être connectée au corps du patient ;
- un tuyau interne (1), inséré dans ledit tuyau externe, présentant une paroi interne , une paroi externe et deux extrémités fixées, sur toute leur circonférence, au tuyau externe (2), sur toute sa circonférence, le flux sanguin circulant au travers dudit tuyau interne (1);
- la paroi externe du tuyau interne et la paroi interne (1) du tuyau externe (2) définissant un espace (3) destiné à être rempli de fluide, ledit espace (3) étant relié par un port connecteur (4) à un appareil permettant de créer un (des) gonflements/dégonflements dudit espace (3) entraînant la création de pulsation(s) du flux sanguin.

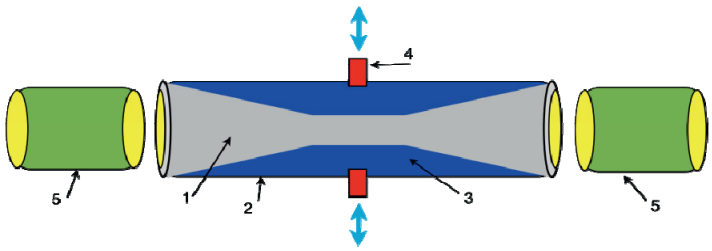

Schéma 8 : Tube pulsatile [3,4]

3. Cathéter pulsatile:

Un dispositif médical pulsatile comprenant (Schéma 9):

- un cathéter, destiné à être inséré dans un vaisseau sanguin, ayant un diamètre et présentant une tige à son extrémité d'insertion, dite partie A, et,
- un élément gonflable logé autour d'une partie du cathéter, dite partie B, ledit élément gonflable étant destiné à être relié à un moyen de gonflage placé du côté de l'autre extrémité dudit cathéter, dite partie C, et permettant le gonflage/dégonflage dudit élément gonflable, de manière pulsée caractérisé en ce que le diamètre de la partie B du cathéter est inférieur aux diamètres des parties A et C du cathéter et en ce que les diamètres des parties A et C dudit cathéter sont sensiblement égaux.

Cette diminution du diamètre de la partie B du cathéter permet que le diamètre de l'ensemble partie B du cathéter plus élément gonflable soit diminué par rapport à celui des cathéters de l'art antérieur. Ainsi, lors de l'insertion du cathéter dans le vaisseau sanguin d'un patient, il n'y aura pas trop d'élargissement dudit point d'insertion dû à un diamètre nettement supérieur d'une partie du cathéter.

Dans un mode de réalisation particulier de l'invention, *le diamètre de la partie B du cathéter plus l'élément gonflable à l'état dégonflé est égal ou inférieur aux diamètres des parties A et C du cathéter.* Dans ce mode de réalisation, l'insertion du cathéter n'entraîne aucun élargissement du point d'insertion, ce qui est encore plus avantageux.

De préférence, *l'élément gonflable est formé d'un matériau radio-opaque, biocompatible*. Dans une forme d'exécution particulière, *ledit matériau est du polyuréthane*, ce matériau est un exemple, parmi d'autres, de matériau organique avantageux.

Dans un mode de réalisation particulier de l'invention, *le diamètre du cathéter est de quelques millimètres ou moins*. Ces dimensions correspondent à de petits cathéters utilisés en pédiatrie mais également chez l'adulte pour atteindre certains petits vaisseaux sanguins.

L'invention concerne également un *ensemble médical pulsatile comprenant un dispositif pulsatile, tel que décrit ci-dessus, et un moyen de gonflage comprenant :*
- une poche, adaptée à être remplie de fluide,
- des moyens de compression de poche, adaptés à comprimer ladite poche de manière pulsée ; et
- un moyen de connexion reliant ladite poche audit élément gonflable du cathéter et permettant la circulation du fluide entre ledit élément gonflable et ladite poche.
Cet ensemble médical pulsatile est simple d'utilisation et peu onéreux. De plus, de par sa taille réduite, il est portable. Dans une forme d'exécution particulière de l'ensemble médical pulsatile, *les moyens de compression de poche sont commandés électromécaniquement*.

Dans une forme d'exécution particulière de l'ensemble médical pulsatile, *le dispositif pulsatile et le moyen de gonflage sont d'un seul tenant*.
Le dispositif pulsatile de l'invention, est constitué d'un cathéter, qui est un tube creux, présentant trois parties successives A, B et C. La partie A, également appelée tige, est la première à être insérée dans le vaisseau sanguin du patient. La partie B du cathéter présente un renfoncement dans la paroi externe. Ce renfoncement s'étend sur la longueur B et est présent sur l'entière circonférence du cathéter. Du fait de la présence de ce renfoncement, alors que les parties A et C du cathéter présentent sensiblement le même diamètre, la partie B est, quant à elle, de diamètre inférieur. Un ballon, gonflable, est placé de la même manière que dans l'art antérieur, c'est-à-dire, par exemple, par soudage dans le renfoncement du cathéter. Le renfoncement est tel que le diamètre de la partie B du cathéter munie du ballon à l'état dégonflé est alors sensiblement égal aux diamètres des parties A et C. A l'intérieur du cathéter est inséré un guide métallique. Un port connecteur de fluide, intégré dans la paroi du cathéter, met en communication le ballon gonflable et un moyen de gonflage représenté schématiquement, sur les figures et, du côté de l'extrémité, ce moyen de gonflage pouvant être une console.
A la figure 9, le ballon est à l'état dégonflé, de ce fait le diamètre de la partie B du cathéter avec le ballon à l'état dégonflé est sensiblement égal au diamètre des parties A et C du cathéter.

A la figure 9 le ballon est à l'état gonflé, le diamètre de la partie B du cathéter avec le ballon à l'état gonflé est alors supérieur au diamètre des parties A et C du cathéter.

L'insertion du dispositif pulsatile de l'invention va maintenant être décrite. On pique un vaisseau sanguin du patient avec une aiguille ce qui crée une ouverture, ou point d'insertion. Le guide métallique est alors mis en place. Puis le cathéter est inséré au travers de cette ouverture grâce au guide. Les parties A, B et C du cathéter passent successivement au travers de cette ouverture, n'entraînant aucun élargissement de ladite ouverture puisque, comme dit plus haut, les parties A et C et la partie B, munie du ballon à l'état dégonflé, ont sensiblement le même diamètre. Une fois que le cathéter est en place, c'est-à-dire une fois que le ballon occupe la région du vaisseau sanguin devant être traitée, le point d'insertion est alors parfaitement comblé par la partie C du cathéter et l'écoulement sanguin est ainsi réduit voire annulé.

La figure 9 représente le cathéter relié à une forme d'exécution particulière de moyen de gonflage « D ».

Ce moyen de gonflage D comprend :

- une première partie incluant une poche remplie de fluide, reliée à une extrémité au port connecteur de fluide et à son autre extrémité à une valve anti-reflux, et
- une deuxième partie incluant un moyen de compression « E » de ladite poche comprenant un compartiment compresseur de poche et une commande, par exemple, électromécanique dudit compartiment compresseur. Le compartiment compresseur de poche « E » est schématisé sous une forme grossièrement rectangulaire avec deux grands côtés C1 et l'un des petits côtés C2 ouvert tandis que le second C3 est relié à la commande électromécanique représentée schématiquement par un triangle. Le compartiment compresseur présente donc un évidemment.

On place le cathéter de l'invention dans un vaisseau sanguin d'un patient, comme décrit ci-dessus. L'extrémité du port connecteur de fluide faisant saillie hors du corps du patient est connectée à la poche. La poche est alors remplie de fluide (qui peut être de l'hélium, du dioxyde de carbone, du sérum physiologique) par ouverture de la valve (cette opération pouvant avoir été effectuée avant la connexion du port connecteur de fluide à la poche). La poche est ensuite placée dans l'évidemment du compartiment compresseur commandé par la commande électromécanique. Selon

les instructions reçues par ladite commande électromécanique, un rythme précis de pression/décompression de la poche se met en place, ce rythme pouvant être, par exemple, de 10 à 300 pressions par minute. La compression de la poche entraîne un flux de fluide en direction du ballon qui se gonfle et la décompression de la poche entraîne un appel de fluide du ballon vers la poche, ce qui dégonfle le ballon. Un mouvement de pulsation du fluide est ainsi transmis de la poche jusqu'au ballon. Cet ensemble cathéter-ballon-moyen de gonflage forme donc un ensemble médical pulsatile portable. En effet, le moyen de gonflage comprenant la poche, le compartiment compresseur de poche et la commande électromécanique, est facilement transportable par le patient lors de ses déplacements, ce qui lui permet de garder une certaine mobilité.

Ce moyen de gonflage est de faible coût et d'utilisation simple. En effet, la compression/décompression ne nécessite pas de source de pression coûteuse au contraire des consoles des ballons intra-aortiques de l'art antérieur.

Les dispositifs pulsatiles de l'invention pouvant s'appliquer aux cathéters de petit diamètre, on disposera de petits cathéters pulsatiles, ce qui n'est actuellement pas le cas. Ces petits cathéters pulsatiles pourront être utilisés dans de nombreuses applications.

En effet, le gonflement du ballon, placé dans un vaisseau sanguin, augmente la force de cisaillement sur la paroi du vaisseau sanguin.

Ces petits cathéters pulsatiles pourront donc être utilisés non seulement pour traiter des artères coronaires bouchées (le petit diamètre du cathéter permettant d'atteindre la région bouchée de l'artère et le mouvement pulsatile du ballon permettant de traiter de manière douce ladite région), mais également pour traiter de possibles malformations du fœtus en passant par les vaisseaux ombilicaux. De nombreuses autres applications sont envisageables comme dans l'interdépendance angiogénèse-apoptose (par exemple, augmenter l'angiogénèse en cas de fracture chez une personne agée afin d'accélérer la cicatrisation), l'athérosclérose (coronaire, cérébrale, rénale), le système immun, la cardiogénèse, la sécrétion de monoxyde d'azote (pour traiter, par exemple, l'hypertension artérielle systémique pulmonaire aiguë et surtout chronique).

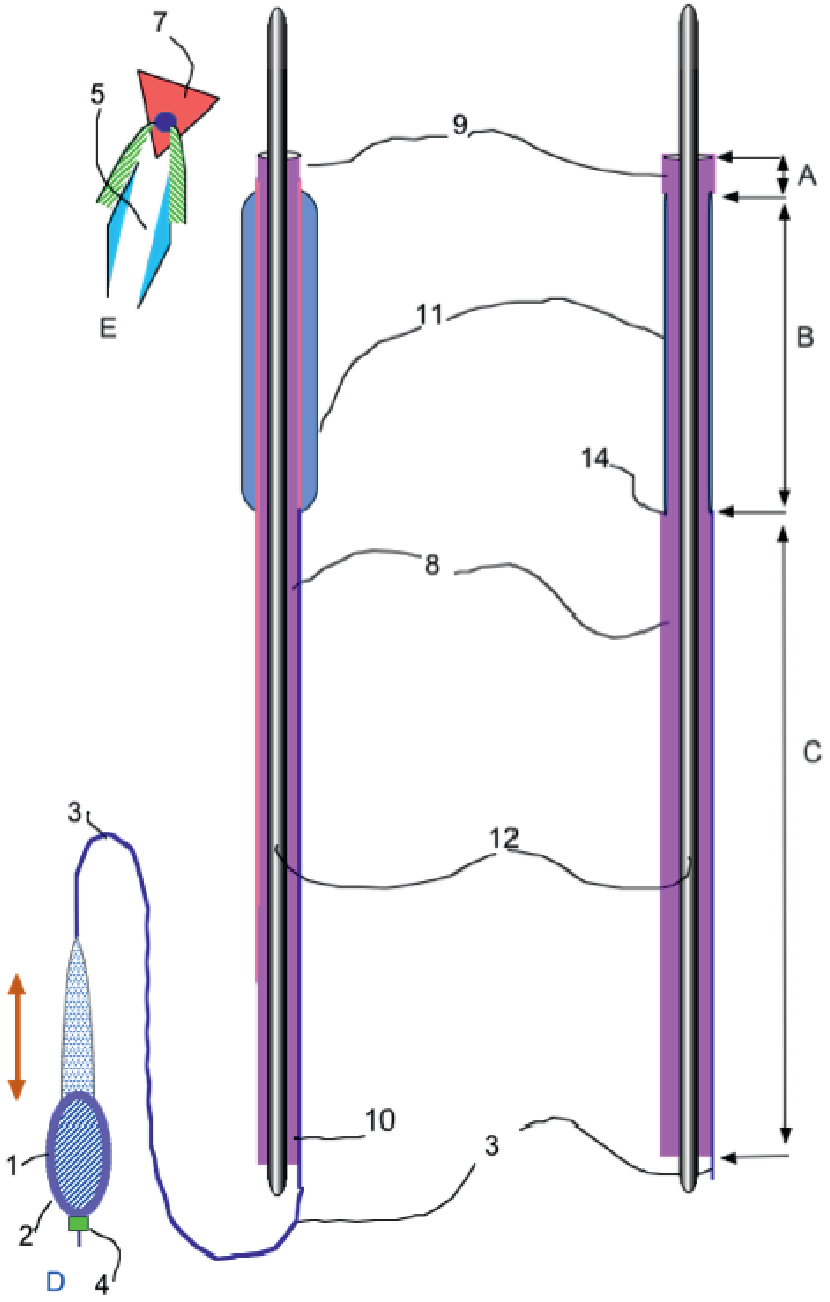

Schéma 9: Cathéter pulsatile [5,6]

4. Console pulsatile :

La présente invention concerne un dispositif médical portable apte à appliquer un fluide sous pression de façon pulsée vers un organe médical, comprenant une cartouche étanche renfermant ledit fluide sous pression. Selon l'invention ladite cartouche coopère avec un carter rigide, et ledit réservoir et/ou ledit carter présentent au moins une entrée munie d'une première valve anti-retour en vue de leur remplissage par ledit fluide ; ledit réservoir et/ou ledit carter rigide présentent au moins une sortie munie d'une deuxième valve anti-retour associée avec une connexion vers ledit dispositif médical.

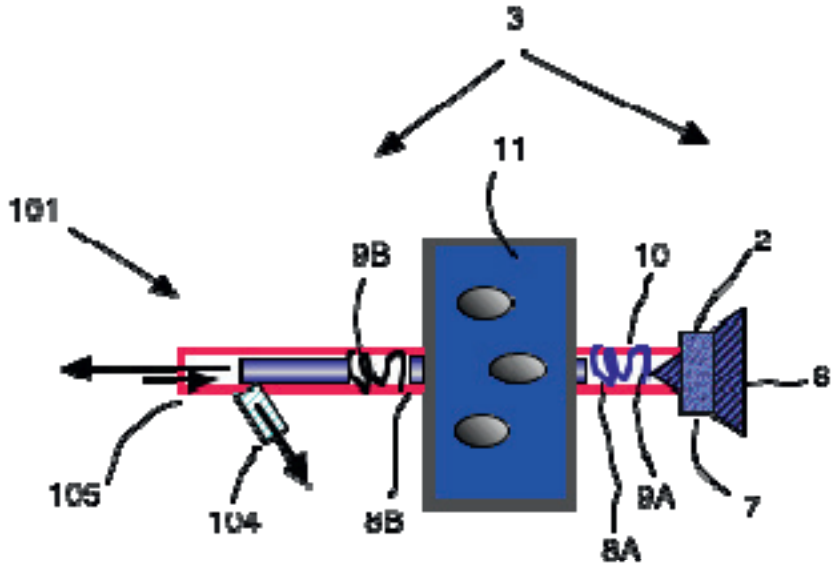

FIG. 1

Schéma 10: Console pulsatile [7]

5. Smartcan :

La présente invention concerne un dispositif médical à usage unique, destiné à être utilisé dans le domaine cardiovasculaire : en chirurgie cardiaque pendant la circulation extracorporelle ainsi qu'avec d'autres systèmes d'assistance cardiaque, en cardiologie interventionnelle ainsi pour toutes indications nécessitantes une voie d'abord cardiovasculaire soit par une canulation ou un cathétérisme des vaisseaux sanguins (anesthésie, réanimation, urgences … etc).

Ce dispositif permet, par exemple, d'obtenir une pénétration des vaisseaux sanguins et cavités cardiaques d'un patient soumis à une chirurgie cardiaque à cœur ouvert à façon plus efficace et sécurisés.

La circulation extracorporelle (CEC) qui est nécessaire pour maintenir la perfusion des organes et les fonctions métaboliques lors de la cardioplégie chirurgicale ou pour assister le muscle cardiaque défaillant jusqu'à sa récupération ou comme relais avant la transplantation.

En générale une console de CEC est composée d'une pompe centrifuge ou péristaltique est utilisée comme pompe de tête artérielle et quatre autres pompes péristaltiques sont utilisées pour l'aspiration de la cardiotomie, la circulation des chambres cardiaques, l'administration de la cardioplégie et une pompe de secours, ainsi que de matériel biocompatible comme les tubulures, les canules artérielle et veineuse, le réservoir veineux, l'oxygénateur, le filtre artériel, ….

Le relais entre la CEC et le corps humain nécessite du matériel spécifique (tubulures, canules et cathéters) qui s'adapte à la morphologie et critères biophysiques de chaque partie visée du cœur et vaisseaux :

a) la ligne artérielle de la CEC et connectée à une **canule aortique** (ou fémorale) ; b) un retour veineux qui est connecté à 1 ou 2 **canules veineuses**, introduites dans les veines caves supérieure et inférieure ; c) une **canule du décharge** du ventricule gauche introduite par la pointe de cœur, l'oreillette gauche ou l'artère pulmonaire ; d) un **cathéter** pour l'injection de la cardioplégie par introduit dans la racine de l'aorte en amont de la canule aortique, dans le sinus coronaire ou directement dans les ostia coronaires ; e) des cathéters pour les mesures hémodynamiques : ligne de pression **artérielle systémique** ± **pulmonaire**,voies **veineuses** dont une voie centrale, ligne pression oreillette gauche, … .

Techniques chirurgicales :

Cependant, toute action sur le cœur et les vaisseaux est toujours soumise à question car c'est une technique délicat, spécialement chez les nouveaux-nés et les enfants avec des risques hémorragiques et traumatiques plus élevés.

Citons par exemple la canulation aortique, afin de la sécuriser en place, il faudra poser des **points de sutures** en purse gardés sur **tirettes** avant percer l'aorte par une lame de **bistouri**, suivi par enfoncement de la canule rapidement afin d'éviter une hémorragie massive avec des conséquences très graves surtout chez les nouveaux-nés. La canule par la suite sera **raccorder** avec la ligne artérielle de la CEC en prenant toute la précaution pour éviter les embolies gazeuse dans le circuit de CEC. Pareillement on répète le même geste pour mettre en place le cathéter ou la canule de la cardioplégie. L'aorte sera clampée par **clamp aortique qui** sera posé entre l'aorte et le cathéter de la cardioplégie au moment de démarrage de la CEC (le cœur s'arrêtera suite à l'injection de la cardioplégie).

Des méthodes techniquement réservées aux chirurgiens les plus expérimentés, demeurent invasives avec des complications vasculaires considérables, qui laissent souvent une zone de manœuvre chirurgicale très limitée si on rajoute un geste opératoire sur l'aorte. Particulièrement chez les nouveaux-nés avec une racine aortique très courte, ou chez les personnes âgées avec une aorte en porcelaine ce qu'augmentent les risques chirurgicaux : dissection artérielle, syndrome thromboembolique, fractures des plaques d'athéromes.

En conclusion, les méthodes citées ci-dessus ne résolvent donc pas les effets indésirables de la chirurgie cardiovasculaire,

Afin de résoudre cette difficulté technique et ses conséquences, les inventeurs ont proposé une solution plus efficace qui doit répondre à chaque problème imposé pendant la canulation vasculaire étape par étape.

Cette solution consiste en une seule ***Canule Intelligente*** **(SMARTCAN),** qui regroupe tous les outils et les moyens indispensables pour obtenir une voie d'abord cardiovasculaire à façon plus efficace, rapide, à bas coût et en toute sécurité.

Le dispositif **SMARTCAN,** prévu en plusieurs versions à usage unique: a) canule aortique, b) canule cardiaque, c) cathéters vasculaires, d) tubulures de drainage cavitaire (thoracique, … etc), obtiendra (Schéma 11):

- **Un système de fixation,** qui remplacera le plusieurs sutures en purse et ses tirettes ;
- **Un système d'obstruction du flux sanguin,** qui remplacera le clamp aortique métallique que provoque sans aucun doute un traumatisme vasculaire surtout sur la partie endothéliale de la paroi intérieure **;**
- **Un système de perfusion guidée,** qui remplacera le canule de la cardioplégie, et dirigera la perfusion sanguine et cardioplégique séparément à façon plus précise et efficace **;**

En plus des tous ses avantages, ces-ci laissera plus d'espace chirurgical sur l'aorte pour bien aborder le cœur plus à façon plus à l'aise et sécure.

Le dispositif de l'invention **«SMARTCAN»** comprenant : a) une partie dite proximale dans laquelle : **un système de disquettes (ballonnets) gonflables** a été intégré de façon extra-lumen, **plusieurs foramens** (trous), dont un central ; b) une partie dite intermédiaire qui représente le corps du tube avec une **longueur et diamètre variables** qui correspondant aux géométries cardiovasculaires, ainsi aux applications (indications) cliniques, un **système de commande «NSS»**; **tiges des cathéters** intégrés aux corps connectant la partie distale et proximale, **tige du guide métallique ;** c) partie dite distale : sécurisée par un système des valves à sens unique.

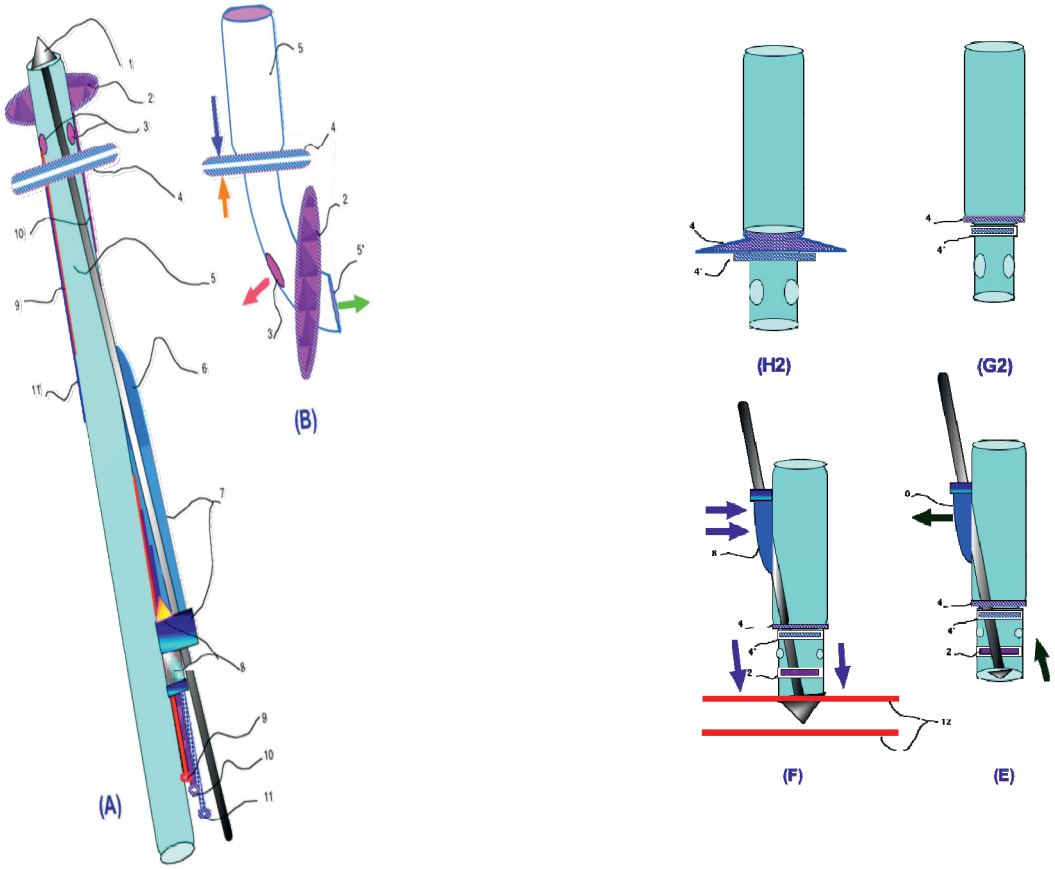

Schéma 11: Smartcan [8]

6. L'Orthèse cardiaque :

La présente invention concerne une méthode thérapeutique destinée à améliorer l'hémodynamique, la microcirculation globale dans les organes, à restaurer et à préserver la fonction endothéliale déficiente chez un être humain malade, comprenant les fonctions suivantes (Schéma 12):

- Maintenir en circulation du sang dans les veines et artères du malade
- Décharger temporairement le cœur de sa fonction de pompe
- augmenter la précharge du ventricule droit afin d'améliorer l'oxygénation du myocarde et sa contractilité et/ou
- produire et diffuser des pulsations régulières à proximité de la racine aortique afin d'améliorer l'hémodynamique du ventricule gauche du cœur et/ou
- stimuler mécaniquement l'endothélium par des forces de cisaillement afin de diminuer la postcharge systémique et pulmonaire.

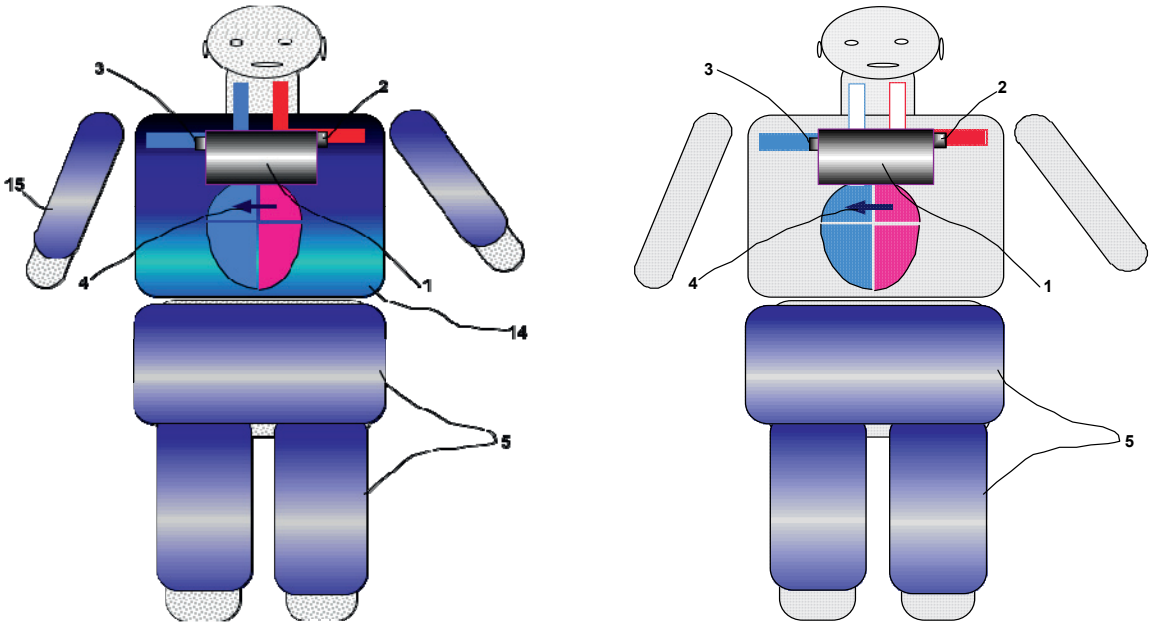

Schéma12: L'Orthèse cardiaque [9]

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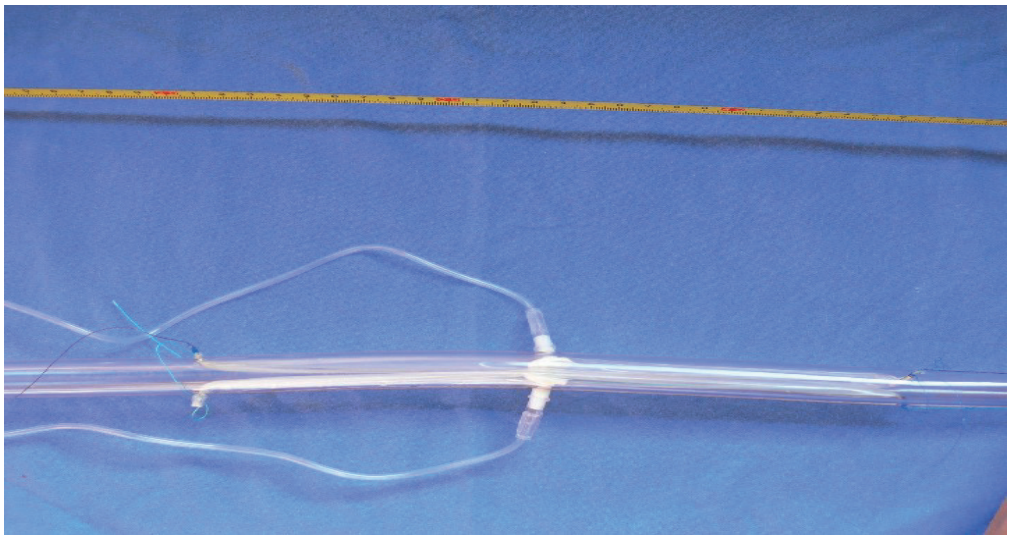
Prototypes

1) Combinaison pulsatile

Figure 7: Masque pulsatile (droit), pantalon pulsatile (gauche).
Image en bas: Pantalon pulsatile (séance d'exercise physique)

2) Tube pulsatile

Première option: un système du compression interne du flux sanguin, avec l'avantage de supressions de raccords de connections. Ce système et applicable uniqument pour la CEC.



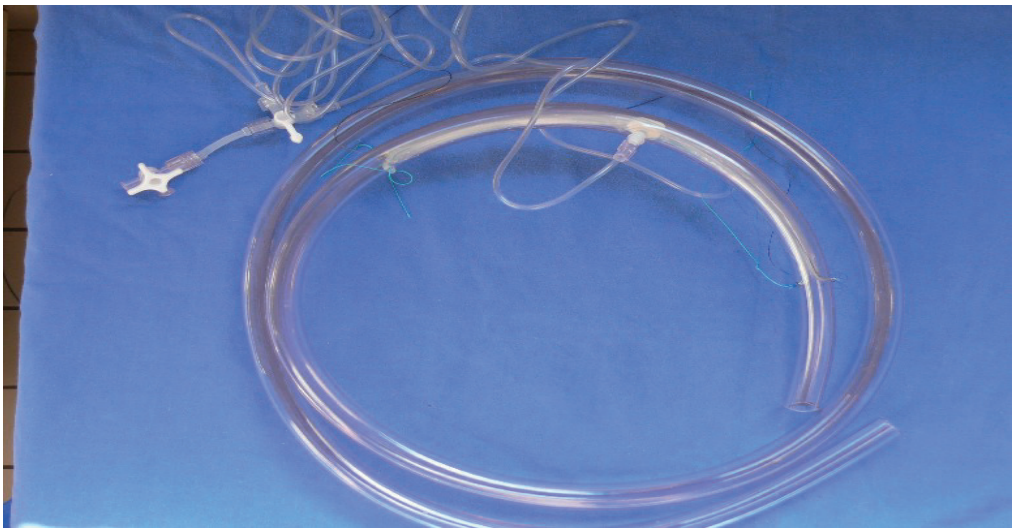


Figure 8: Premiers prototypes du tube pulsatile, en fixant les ballonnets des deux cathéters de contrepulsion aortiques à la parois intérieure d'un tuyau du circuit de CEC (3/8 pouce) (Dr. Nour)

2ème option: Un système de compression extreme du flux sanguin, avec l'avantage de ne pas avoir la necessité de l'utilisation du gas inerte, reductions de pertes de charges energetiques et la possibilité de ses applications avec le CEC et DAC.

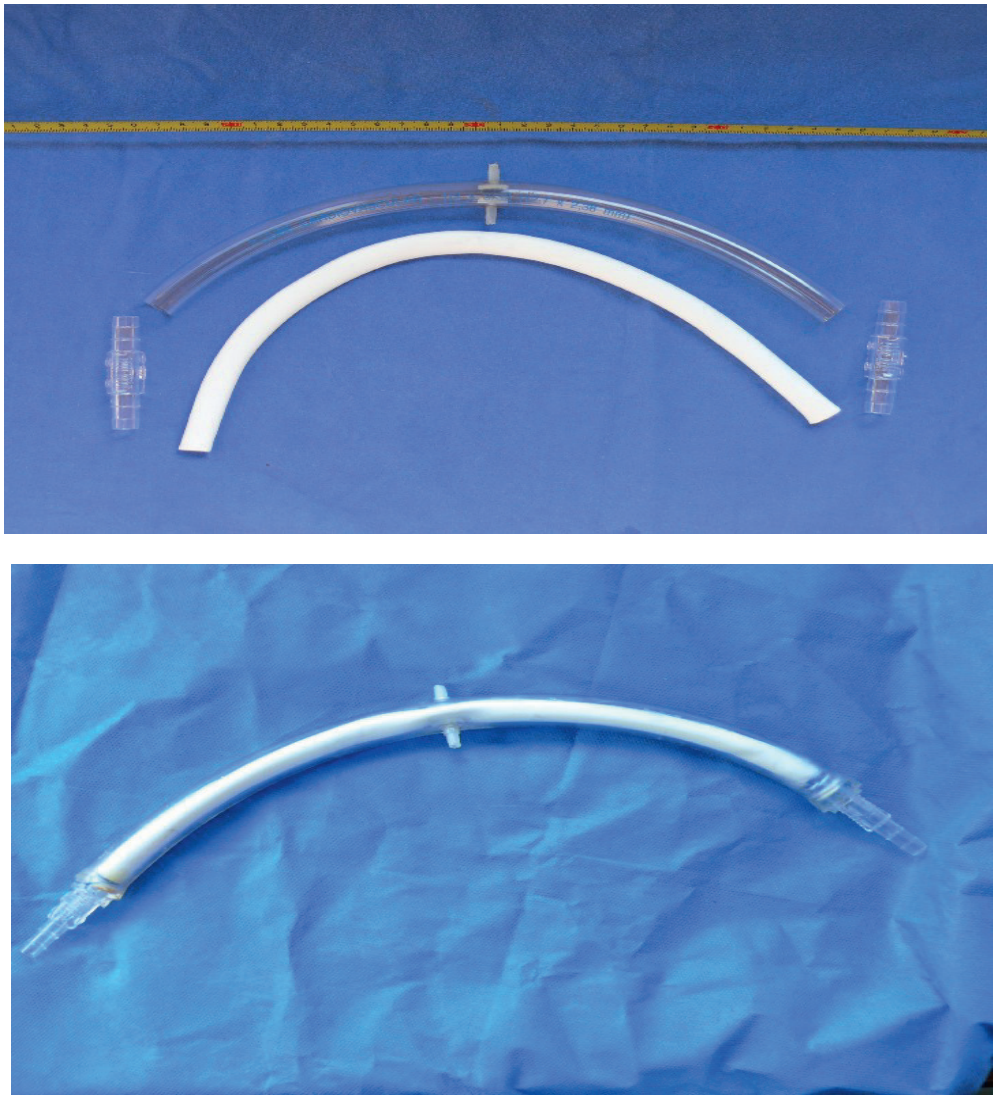
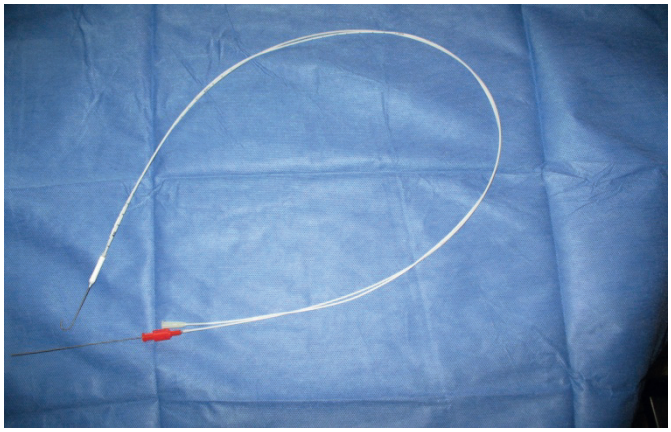


Figure 9: Prototype du tube pulsatile en utilisant un tube interne flexible (PTFE), et extremité rigide (PVC), (Dr. Nour)

3) Cathéter pulsatile :



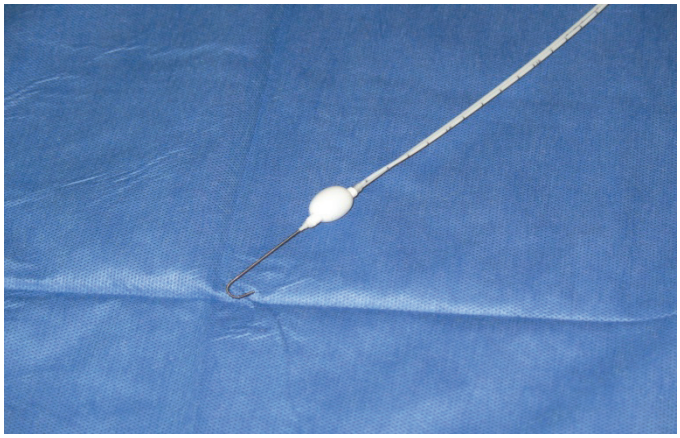


Figure 10: Prototype du cathéter pulsatile

4) Console pulsatile:

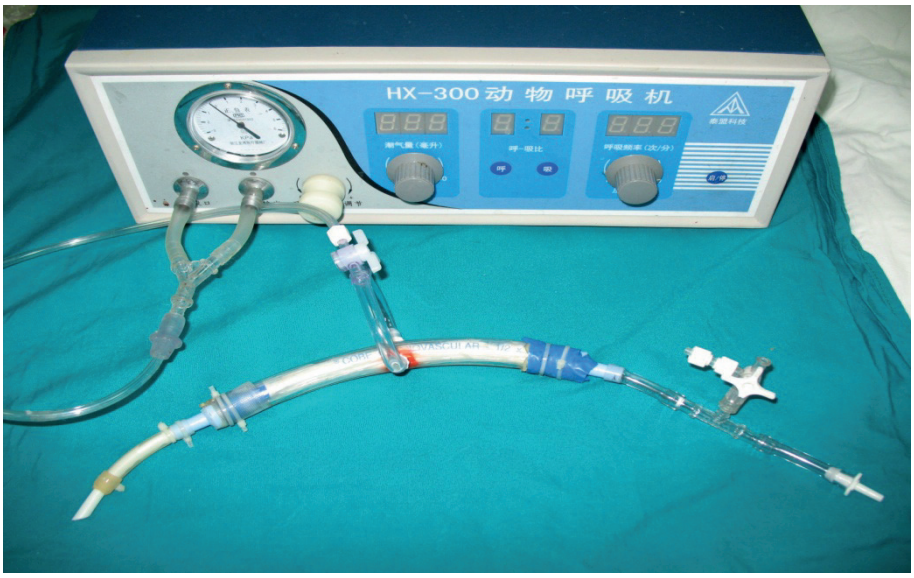


Figure 11: Prototypes de console pulsatile

image en haut Un ventilateur de rat, utililsé comme un génerateur pulsatile (Dr. Nour)

Image en bas: Console pulsatile pour le masque (University Sun Yat Sen)

5) Smartcan:

Figure 12: development en cours

6) L'orthèse cardiauqe

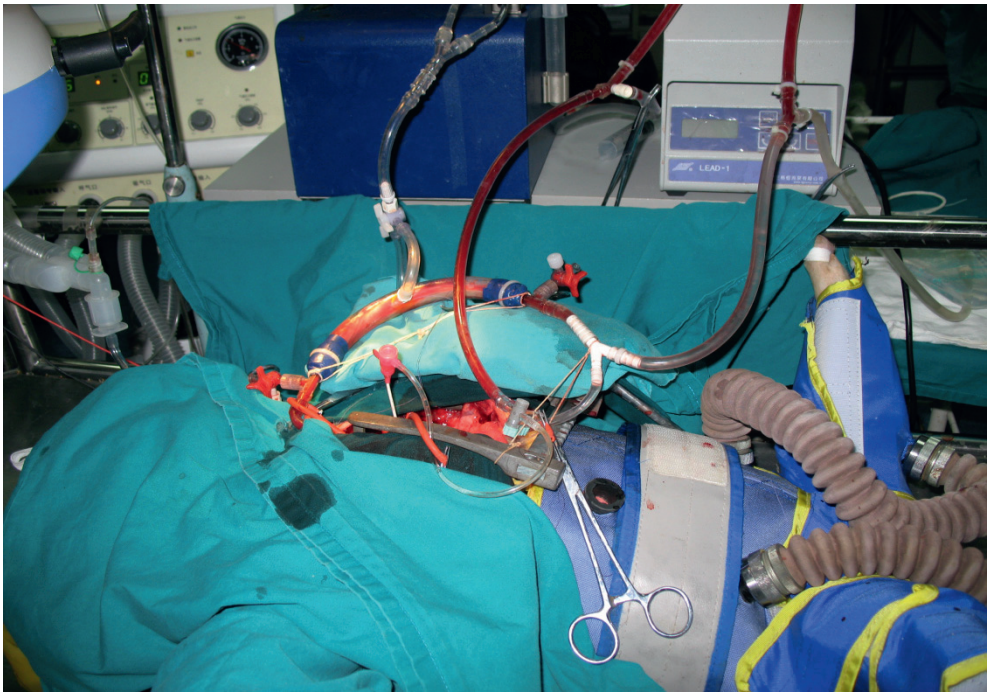


Figure 13: L'Orthèse cardiaque (image opératoire)

Part II

Études expérimentales

Chapitre V

Études expérimentales

I. Tubulure pulsatile : études effectuées in vitro et in vivo.
II. Cathéter pulsatile : études in vivo.
III. Combinaison pulsatile : études in vivo et préclinique.

Les prototypes des dispositifs d'assistance circulatoire ont été évalués in vitro, in vivo ainsi en préclinique.

Les étude in vivo ont été approuvées par le règlement pour la recherche des animaux à Sun Yat-Sen University et conforme au Guide pour le soin et l'utilisation des animaux de laboratoire (NIH Publication n ° 85-23, révisée en 1996).

Dans des modèles animaux originaux, nous avons créé un état de choc cardiogénique aigu chez des porcelets.

Nous avons évité toute prémédication, traitement prophylactique ou tout autre action médicale qui peut interférer avec la fonction endothéliale (par exemple atropine, les bêtabloquants, etc.). Seule une assistance cardiaque mécanique a été fournie avec l'appareil évalué par rapport aux thérapies traditionnelles dans les groupes témoins. Les bénévoles pour les études précliniques étaient des collègues médecins.

Afin d'éviter inutilement, la répétition des sujets, nous présentons dans ce chapitre un sommaire de chaque étude qui sera plus détaillée dans la 3ème partie de cette thèse en correspondance de sa publication.

1. **L'évaluation du dispositif du tube pulsatile*:**

Les perfusions du système cardiovasculaire avec des dispositifs tels que le circulation extracorporelle (CEC) et l'assistance cardiaque mécanique (DAC) perturbent la fonction endothéliale, qui est responsable du syndrome de post-cardiotomie.

Cette dysfonction endothéliale est très probablement en rapport avec le caractère continu du flux continu qui suppriment la force de cisaillement endothéliale, ajouté aux pertes de charges énergétiques dans les circuits.

Pour surmonter ces effets différentes stratégies thérapeutiques sont actuellement appliquées, tels que: a) prise en charge pharmacologique par antifibrinolytique, inotropes, vasodilatateurs, les plaquettes, etc., mais avec une certaine effets secondaires ainsi; b) normothermie; c) recours minimal à la CEC qui reste encore une technique difficile réservée à des groupes sélectionnés de patients; d) la CEC pulsatile avec ses avantages prouvés cliniquement et expérimentalement. En revanche, des études récentes recommandent du système de perfusion conventionnel. Ceci s'explique par l'incapacité d'une CEC pulsatile à produire des courbes adéquates à cause des pertes des charges énergétiques par l'oxygénateurs.

L'association d'une pompe de contrepulsion intra-aortique (CPIA) avec une CEC conventionnelle, crée des zones de turbulences, avec des complications vasculaires et l' efficacité de la perfusion des organes est controversée.

Alternativement, des prototypes de tube pulsatile ont été évalués comme une solution potentielle pour ces inconvénients liés à la circulation extracorporelle (CEC) et l'assistance cardiaque mécaniques (DAC).

Matériels et Méthodes

1.1. Étude in vitro:

Des prototypes du tube pulsatile ont été positionnés dans trois simulations d'un circuit de CEC pédiatrique (¼ de pouce ; 1.5 m de ligne artériel ; 1.5 m de ligne veineux), composée d'une tête de pression (pompe à galet) classique, oxygénateur à membrane, un filtre artériel, une canule aortique (14 Fr.), et une simulation de résistance vasculaire par un clamp partiel du tuyaux retour veineux. Le circuit a été rempli par un volume d'amorçage composé du sang (2/3) prélevé la veille chez un porc et de sérum héparine (1/3).

Le tube pulsatile a été placé à 6 cm de canule aortique (circuit I) ; à 150 cm de canule aortique (circuit II) ; et entre la tête de pression et l'oxygénateur (circuit III). Avec des débits variés entre 400, 600, 800 et 1000 mL/min, et une fréquence pulsatile fixe (110 bpm), nous avons comparé le flux continu et pulsatile afin d'évaluer les pertes de charges énergétiques à partir de lignes de pressions positionnées en amont et aval: l'oxygénateur, le tube, la canule aortique et la simulation de résistance vasculaire.

Statistiques

Les variables continues sont exprimées comme la moyenne SEM ±. Les comparaisons entre les groupes d'échantillons indépendants ont été effectués avec Student t-test, pour les données hémodynamiques in vitro et une analyse de variance 2-way ANOVA pour les données in vivo. P avec une valeur inférieure à 0,05 a été considérée comme statistiquement significative. Un logiciel (GraphPad Prism ®) a été utilisé pour toutes les analyses statistiques de cette étude.

Résultats

- Le débit moyen pulsatile était significativement ($p<0.05$), meilleur que le débit continu dans tous les circuits (I, II et III).
- Les pertes de charge ont été augmentées dans les circuits III et II par rapport à I.
- La pression différentielle a été augmenté de façon significative avec le circuit I (126,3 ± 18,6) par rapport aux circuits II (66 ± 6,1) et III (48,8 ± 4,7), respectivement (mmHg, $p <0,001$).

1.2. Étude in vivo:

Le dispositif du tube pulsatile a été évalué chez dix porcelets divisés en deux groupes : pulsatile (P, n: 5), et non-pulsatile (NP, n = 5). Sous anesthésie, ventilation mécanique, sternotomie et injection d'une dose d'héparine (2.5 mg/kg) : dans le groupe P, un prototype du tube pulsatile a été connecté à un système d'assistance ventriculaire gauche conventionnel, composé d'un pompe à galet, une canule aortique (12 Fr.) et une canule de décharge ventriculaire gauche (14 Fr.). Dans le group NP, la canule aortique (12 Fr.) et la canule de décharge gauche (14 Fr.) ont été connectées à une pompe centrifuge conventionnelle.

Dans le group P, les longueurs de deux canules aortique et décharge ont été raccourcis, afin de diminuer les pertes de charges énergétiques. Une défaillance ventriculaire gauche aigué a été crée par une ligature de l'artère coronaire interventriculaire antérieure (IVA) après la bifurcation de 2ème diagonale. La phase thérapeutique a été démarrée aux premiers signes de détérioration hémodynamique, pour une période de 2 h, dans les deux groupes. En groupe P, la fréquence du tube pulsatile a été fixée à 90 bpm, et un débit de perfusion au tour de 0.3 L/min. Dans le group NP, le débit de la pompe centrifuge a été fixé à 0.8 L/min.

Résultats

- Une amélioration significative de l'hémodynamique avec une disparition macroscopique de la zone ischémique ont été observée dans le groupe P par rapport du groupe NP.
- Le débit cardiaque était de 0,67 ± 0,26 dans le group P versus 0,38 ± 0,03 dans le group NP (L / min; p> 0,05).
- Les résistances vasculaires systémiques étaient 451,72 ± 24,01 dans le groupe P versus 1309,88 ± 151,93 dans le groups NP (dynes.s.cm^{-5}/kg^{-1}; p <0,001).

Conclusion

Le tube pulsatile peut être adapté aux circuits des appareils de perfusion cardiovasculaires conventionnels, afin de maintenir la fonction endothéliale par les forces de cisaillements. Ceci pourra améliorer l'hémodynamique et reduire les pertes de charges énergétiques, avec une méthode à coût bas qui favorise une faible mortalité et de morbidité.

Soumis pour publication (Chapitre VII).

2. **Évaluation du dispositif du cathéter pulsatile:**

   Des prototypes ont été testés dans deux études sur de modèles animaux pour les traitements de l'infarctus aigu du myocarde et l'hypertension artérielle pulmonaire aigue comme suit:

2.1. Modèle d'infarctus aigu du myocarde* :

Position du problème : La maladie cardiaque ischémique est une cause importante de mortalité liée aux faibles possibilités thérapeutiques incapables de corriger l'insuffisance fonctionnelle endothéliale sous jacente. Pour surmonter ces limitations nous proposons donc de mettre en œuvre un nouveau traitement utilisant un cathéter pulsatile intravasculaire pulmonaire qui , en augmentant de façon contrôlée les forces de cisaillement intravasculaire, renforce l'homeostasie vasculaire pulmonaire endothélium dépendante.

Matériels et Méthodes :

Deux groupes de 6 porcelets sont étudiés ; après sternotomie on réalise une ligature de la coronaire ascendante gauche dans chacun des 2 groupes expérimentaux respectivement pulsatile (P) et non pulsatile (NP). Après une heure d'ischemie chez les animaux héparinés on introduit un cathéter à balonnet pulsatile dans le tronc de l'artère pulmonaire des animaux du groupe P ; le cathéter sera pulsé de façon intermittente pendant 1 heure a la fréquence de 110 pulsations par minute quelle que soit la fréquence cardiaque. Le groupe NP recevra seulement un traitement pharmacologique (Trinitrines; 7±2mg/kg/min IV).

Résultats :

On obtient une survie post-ischémique de 120 min. dans le groupe P contre 93 min. dans le groupe NP. On observe une amélioration du débit cardiaque du groupe P à 0,92±015 L/min. contre 0,52±0,08 L/min dans le groupe NP et la différence est significative ($P<0,05$). Les résistances vasculaires pulmonaires sont significativement plus basses dans le groupe P que dans le groupe NP (119±13 vs 400±42 dynes.sec/cm-5/kg) et la différence est statistiquement significative. les résistances vasculaires systémiques sont de 319±43 pour le groupe P contre 1857±326 dans le groupe NP. La quantification de l'apoptose dans le tissu myocardique donne un chiffre de 0,66±0,07 dans le groupe P contre 4,18±0,27 dans le groupe NP.

L'expression des ARN messagers myocardique pour la NO synthase est plus importante dans le groupe P (0,90±0,09) que dans le groupe NP (0,25±0,04).

Conclusion :

Dans l'ischémie myocardique aigue la mise en œuvre d'un dispositif pulsatile approprié permettant de moduler les forces de cisaillement sur l'endothélium vasculaire pulmonaire permet d'obtenir une bonne stabilisation hémodynamique. La mise en œuvre de cette technique peut coûteuse permet d'enrichir l'arsenal thérapeutique dans le traitement de l'ischemie myocardique aigue au prix d'une faible morbidité et mortalité.

* Soumis pour publication : (Chapitre VIII).

2.2. **Modèle d'hypertension artérielle pulmonaire aigue* :**

But du travail : L'hypertension artérielle pulmonaire (HTAP) peut être l'expression une altération fonctionnelle de l'endothélium conduisant à augmentation des résistances vasculaires pulmonaires de mauvais pronostic. L'arsenal thérapeutique reste encore limité. Nous proposons de développer un nouveau dispositif pulsatile offrant de meilleures perspectives thérapeutiques comparées aux options actuellement disponibles. *Matériel et méthodes* : 12 porcelets (10,3±3,8 kg) sont soumis à une stimulation pulsatile intravasculaire pulmonaire (groupe P ; n=6) ou reçoivent un traitement par le Tadalafil. Après sternotomie médiane les animaux sont héparinés (250UI/ kg)et on réalise chirugicalement un shunt aortopulmonaire pendant 1 heure. Ensuite, dans le groupe P, notre prototype de cathéter pulsatile a ballonnet est introduit dans le tronc de l'artère pulmonaire, et pendant une heure le ballonet est soumis à un cycle inflation-déflation à une fréquence de 110 cycles par minute (au moyen d'un ventilateur pour petits animaux) quelque soit la fréquence cardiaque(90,6±10,7). Le group NP est traité par du Tadalafil (1mg/ kg per os). Les résultats hémodynamiques ainsi que le débit cardiaque (DC) sont meilleurs dans le groupe P que dans le groupe NP ($P < 0,05$) : DC respectivement 0,56±0,26 vs 0,54±0,11 L/min. La pression artérielle pulmonaire moyenne est plus basse dans le groupe P que dans le groupe NP : soit respectivement 9,6±2,9 vs 32,2±5,1 mmHg. Les résistances vasculaires dans le groupe P sont également plus basses que dans le groupe NP : les résistances vasculaires pulmonaires sont respectivement de 85±42 vs 478± 192 et les résistances vasculaires systémiques respectivement de 299 ±173 vs 1301±616 dynes.s.cm-5/kg. L'analyse par Western blot de l'expression de la NO synthase dans les artères pulmonaires montrent que cette dernière est plus importante dans le groupe P que dans le groupe NP mais la différence n'est pas statistiquement significative (respectivement 0,81 ± 0,78 vs 0,62 ± 035 ; $P>0,05$).

Conclusion : la modulation de la fonction endothéliale induite par les forces de cisaillement intravasculaire contrôlées par un dispositif intravasculaire pulsatile adapté, constitue une approche thérapeutique efficace de l'hypertension artérielle pulmonaire mettant en jeu des mécanismes proches de ceux rencontrés dans l'homéostasie vasculaire physiologique.

* Publication : *Pediatric Cardiology Journal* (Chapitre VIII).

3. Évaluation du dispositif de la combinaison pulsatile :

Abstract* :

Position du problème : La défaillance cardiaque droite est un trouble fréquent en cardiologie pédiatrique. Malgré l'utilisation d'agents chronotrope et inotrope, le remplissage et l'utilisation d'oxyde nitrique inhalé la défaillance cardiaque droite reste difficile à corriger.

L'utilisation d'un dispositif d'assistance cardiaque adapté à physiologie et la mécanique droite pourrait être plus efficace.

Matériel et méthodes : Nous avons développé un dispositif d'assistance cardiaque non invasive (DAC) utilisable en néonatalogie et en pédiatrie. Il est constitué d'une combinaison pulsatile recouvrant les zones ayant une influence sur le cœur droit. Il sera testé sur un modèle animal néonatal d'insuffisance ventriculaire droite (IVD).

Le plan expérimental comprendra à côté du groupe traité un groupe contrôle et un groupe sham. Les résultats attendus sont une amélioration immédiate de l'hémodynamique en rapport avec une réduction synchronisée de la capacitance veineuse résiduelle, une augmentation de la précharge et de la contratilité. A distance l'augmentation des forces de cisaillement intravasculaires, induites par le dispositif qui contrôle la pression intra thoracique de façon synchrone, va améliorer en la redistribuant la circulation pulmonaire. Des travaux complémentaires porteront sur les aspects hémodynamiques, la pharmacologie et la biochimie vasculaire et enfin les problèmes d'angiogénèse.

Commentaires : Cette technique d'assistance cardiaque droite non invasive assure une meilleure hémodynamique, une bonne préservation de la fonction endothéliale tout en assurant une faible morbidité et mortalité. Cette approche physiologique, à faible coût, semble particulièrement adaptée au traitement de la défaillance cardiaque droite en cardiologie pédiatrique néonatale.

* Publication : *Asian Cardiovas Thorac Ann 2009* (Chapitre IX).

Abstract* :
Position du problème : L'utilisation de dispositifs d'assistance cardiaque droite reste encore contreversée en raison de leur faible efficacité. Ce travail a pour but de tester un dispositif d'assistance cardiaque pulsatile sur un modèle d'insuffisance cardiaque droite et de comparer les résultats obtenus avec les techniques d'assistance classique.
Matériel et méthodes :
Chez 12 porcelets on induit une régurgitation ventriculaire droite par avulsion et transfixation externe de 2 cusps de la valve pulmonaire. Deux groupes d'animaux sont étudiés : un groupe « pulsatile » P et un groupe « non pulsatile NP. La procédure est mise en route dès que l'on observe des signes de défaillance ventriculaire sévère (48± 24min.)
Dans le group P le traitement du pantalon pulsatile a été démarré par un générateur pneumatique à la fréquence de 40 battements par minute. Les animaux du groupe NP ont reçus du Tadalafil (1mg/ kg per os), des solutés de perfusion et de l'adrénaline (0,3 mg/kg en perfusion).
Résultats :
Après une heure d'assistance, le débit cardiaque est significativement meilleur dans le groupe P que dans le groupe NP (1±0, vs 0,7±0,2 2 L /min). La pression ventriculaire droite moyenne (16,6 vs 24,2) et la pression artérielle pulmonaire (22,1 vs 31,2 mmHg) sont meilleurs dans le groupe P.
Les résistances vasculaires sont plus basses dans le groupe P que dans le groupe NP (résistance vasculaire pulmonaire :174,6 vs 352,1 dynes.sec.cm^{-5}.kg^{-1} - résistance vasculaire systémique : 611,7 vs 1215,3 dynes.sec.cm^{-5}.kg^{-1}). L'analyse en Western blot des artères pulmonaires montre une augmentation de l'expression de la NO synthase dans le groupe P.
Conclusions :
Le pantalon pulsatile peut être considéré comme un dispositif non invasif sûr d'assistance cardiaque dans les cas d'insuffisance cardiaque droite aigue.
Il s'agit d'une technique physiologique et peu coûteuse utilisable chez l'enfant comme chez l'adulte.
*Publication : *Asian Cardiovas Thorac Ann*, 2012, (Chapitre IX).

3.1. **Études précliniques du dispositif de combinaison pulsatile***:

Devant la croissance rapide des pathologies à composante ischémique tout comme devant la demande croissante des patients en matière de maintenance de leurs performances physiques, l'amélioration significative de la microcirculation cérébrale et de la microcirculation des téguments (avec interdépendance angiogénèse-apoptose) est promise à un brillant avenir.

Nous déterminerons l'importance de l'augmentation du débit sanguin par rapport à la durée de la stimulation, et sa décroissance dans le temps.

3.1.1. ***Évaluation du Masque pulsatile*:**

Les séances ont été appliquées sur un groupe d'une dizaine de volontaires hommes et femmes chez lesquels la circulation rétinienne (permettant une vision directe de la circulation cérébrale) a été mesurée avant et après stimulation par masque pulsatile.
L'objective du ce protocole de stimulation optimum a été défini afin d'assurer durablement une meilleure vascularisation cérébrale chez les sujets souffrant de pathologies ischémiques et également, après mesure de la microcirculation cutanée, un protocole de stimulation adapté au traitement des troubles trophiques cutanés.
Nous avons démontrés sur l'homme (analyse par Laser Doppler) que les applications du dispositif du masque pulsatile peuvent augmenter significativement la microcirculation dans la région stimulée en utilisant des prototypes artisanaux et être ainsi mis à profit pour améliorer la circulation cérébrale dans le traitement des pathologies aigües et dégénératives à composante ischémique.
La présente étude préclinique avait donc pour but d'utiliser un masque pulsatile appliqué sur la face et la tête pour stimuler le retour veineux et améliorer la microcirculation cérébrale grâce à l'action des forces de cisaillement ainsi stimulées sur l'endothélium vasculaire (capillaire).
Le prototype du masque pulsatile, utilisé dans cette étude a été fabriqué conformément du concept de la combinaison pulsatile, en trois couches de polyuréthane dont la couche intermédiaire a été rempli par de la glycérine, et une couche externe alimentée en flux pulsatile par un générateur pneumatique. L'ensemble du prototype a été couvert par un tissu externe du coton plus résistant qui favorisera la propagation du flux pulsatile vers le visage.

Matériel et Méthode :

Le prototype du masque pulsatile a été testé chez des médecins volontaires sains (n = 8) de deux sexes et compris dans une fourchette d'âge entre 29 et 68 ans. Après 20 minutes de pulsations à basse pression (0,2-0,6 bars) du masque, synchronisé avec le rythme cardiaque diastolique.

Statistiques:

Les variables continues sont exprimées comme la moyenne ± SEM. Les comparaisons entre les groupes d'échantillons indépendants des données hémodynamiques ont été effectuées avec Student t-test. P d'une valeur inférieure à 0,05 a été considérée comme statistiquement significative. Le logiciel GraphPad Prism ® a été appliqué pour toutes les analyses statistiques de cette étude.

Résultats:

L'hémodynamique et le débit sanguin cérébral ont été significativement améliorés (p <0,05), telle qu'elle se manifeste par un écoulement Doppler mesurée à l'artère carotide commune (Figure 35): Débit carotidien: 246 ± 41,73 vs 294 ± 50,42 (ml / min), et la vitesse 18 ± 2,4 vs 21 ± 2,8 (cm / sec).

Microcirculation mesurée de la pointe du nez (Perimed ®-PeriScan 3 Système), était de 45,5 ± 14,6 vs 89,2 ± 31,1 (unités ; p <0,001) avec des pulsations de masque non synchronisées (Figure 4), et de l'angle de la mandibule (mesuré avec Perimed ® - Système Périflux 5000), était de 28 ± 12,5 vs 87 ± 35,2 (unités ; p <0,05), avec des pulsations masque synchronisées (figure 5).

Observation intéressante : comme on le voit sur la figure 4, le débit de la microcirculation a été rapidement augmenté après 15 min de pulsations, puis a diminué légèrement pour passer en plateau au cours des15 minutes de stimulation. Suivantes l'effet physiologique du dispositif, permettant une autorégularisation cellulaire en réponse à la sécrétion de médiateurs vasodilatateurs par l'endothélium, contrairement aux vasodilatateurs exogènes qui peuvent produire un choc hypovolumique à forte dose (par exemple les nitrates).

* Publication : (Chapitre X).

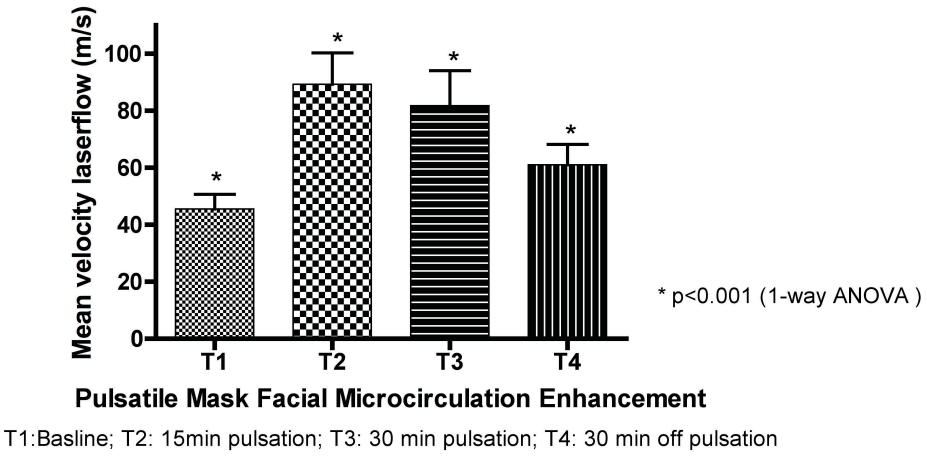


Figure 4: La microcirculation cutanée mesurée de la pointe du nez au départ (T1); après 15 min de la pulsation non-synchronisée avec le rythme cardiaque (T2), à basse pression (0,2-0,4 bar); à la fin (T3), après 30 min de la pulsation. T4: 30 min après l'arrêt de la pulsation.

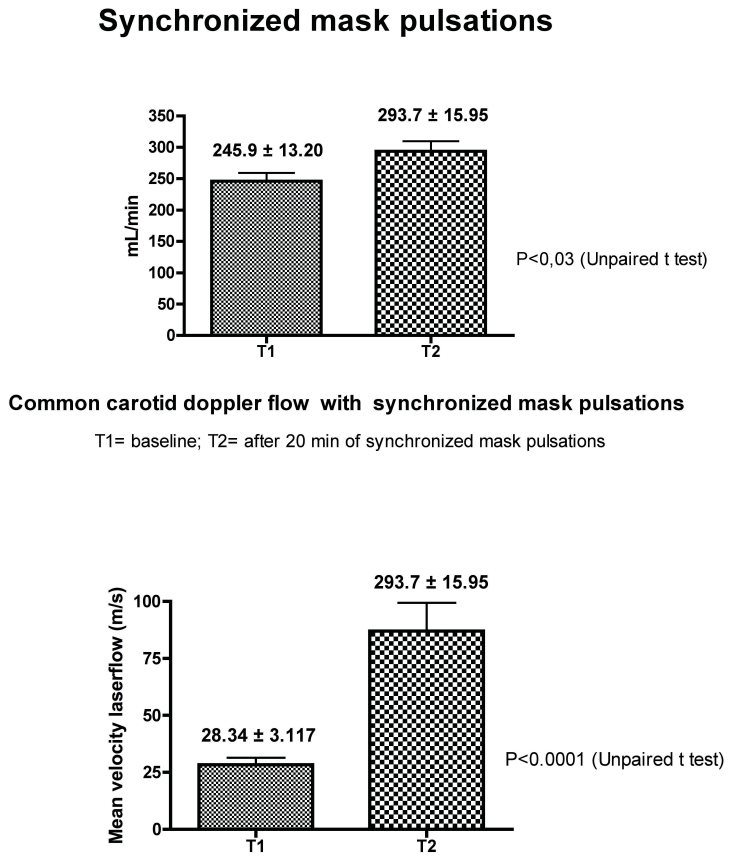


Figure 5 : Panneau supérieur : Flux carotidien mesuré par écho Doppler; panneau inférieur: la microcirculation du visage (à partir de l'angle de la mandibule). T1: de base; T2: après 20 min de pulsations synchronisées

3.1.2. *Évaluation du Pantalon pulsatile** :

Le prototype du pantalon pulsatile a été testé chez des volontaires adultes sains (n=6 ; 29-41 ans). Nous avons appliqués des fréquences pulsatiles fixes (60 bpm), sans synchronisation du rythme cardiaque (72 ± 17 bpm) et à une basse pression (1,2 bar). La microcirculation périphérique a été mesurée avec débitmètre laser (Perimed ®-PeriScan 3 Système) à la pointe du doigt. Résultats (Figure 36); après 20 min de pulsations, la microcirculation a été significativement améliorée: 93,5 ± 31,3 vs 222,4 ± 35,8 (p <0,003).

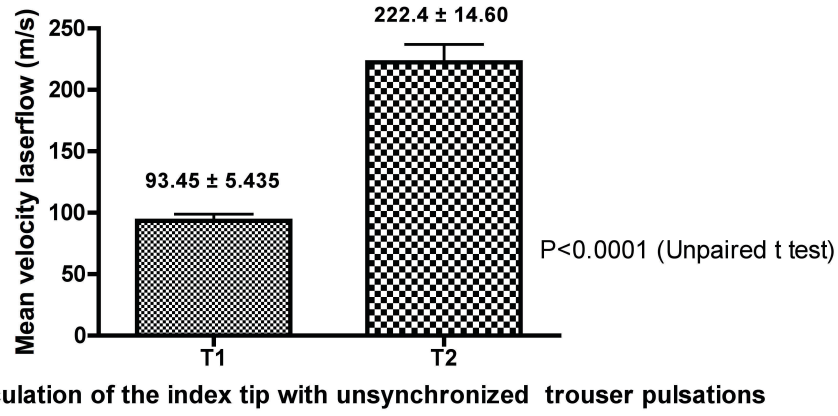


Figure 6 : Augmentation de la microcirculation périphérique, mesurée à la pointe de l'index droit (débitmètre laser: Perimed ®-PeriScan PIM 3 System)

* Publication : (Chapitre X).

4. Évaluation des dispositifs d'assistance cardiaque Bi-ventriculaire **"L'Orthèse cardiaque"** (étude en cours)**:**

4.1. **In vivo***:

l'appareil a été testé dans un modèle d'insuffisance biventriculaire ischémique aigue chez des porcelets pédiatriques.

Il a été créé par ligature milieu de la IVA, et électrocautérisation avec la diathermie des branches de l'artères coronaire droite, pour plus de détails consulter le site ci-joint les films opératoire. Les résultats préliminaires montre de meilleures réponses hémodynamiques avec le dispositif d'assistance biventriculaire peignage du tube pulsatile comme un DAVG et le pantalon pulsatile comme RVAD (Figure 13 ; chapitre IV:pp 99).

Commentaires: dans cette étude l'appareil (l'Orthèse cardiaque) a été testé aussi bien en arrêt cardiaque total, suivie d'insuffisance cardiaque biventriculaire ischémique aigue avec un choc cardiogénique. Le dispositif a été capable de faire circuler les colonnes du sang stagnant dans le respect des conditions physiologiques de chacun des circuits cardiaques (gauche et droit). Le but est de maintenir la force dynamique des flux sanguine et le métabolisme cellulaire en cas de défaillance biventriculaire aiguë jusqu'à l'amélioration de l'hémodynamique ou d'un bridge pour les transplantations cardiaques avec des donneurs compatibles dans un état presque physiologique. L'étude est provisoirement interrompue en attendant la fabrication de nouveaux tubes pulsatiles.

* Publication : (Chapitre X).

4.2. **Évaluation du pantalon pulsatile chez un Patient volontaire * :**

Le pantalon pulsatile, a été testé chez un patient (un médecin du Royaume-Uni), atteint d'insuffisance cardiaque décompensée. Le patient était dialysé 6/7J et en attente des greffes cardiaque et rénal. Il a été retirée de la liste en raison d'une hypertension artérielle pulmonaire sévère (PAP systolique > 65 mmHg), une élévation de BNP (1100 pg / ml), et éjection de fraction 15%.

Comme cela a été demandé par le patient lui-même, comme la seule et dernière chance, le pantalon a été appliqué quotidiennement pendant 20 minutes, en position debout**, avec une fréquence fixe (40 bpm) et quelle que soit la pacemaker patient (78 bpm).

Résultat : Après deux mois : la PAP systolique a été baissée à 41mmHg et le taux du BNP à 500 pg / ml, et augmentation de l'éjection de fraction (20%). L'étude a été interrompue pour des raisons logistiques, ainsi pour une contre-indication formelle: lithiases biliaires qui nécessitent une urgente cholécystectomie afin d'éviter une pancréatite aiguë par les pulsations du pantalon.

* Publication : (Chapitre X).

**Il est préférable de maintenir les patients des insuffisances cardiaque décompensées en position debout, plutôt que la position couchée afin d'amplifier l'effet de gravité comme un facteur d'accroissement de la force de cisaillement avec plus de colonnes volumineuses de la capacitance veineuse.

Chapitre VI

Commentaires

Chapitre VI : Commentaires

Commentaires

Les résultats qui viennent d'être présentés montrent la faisabilité d'une approche originale du traitement des maladies cardiovasculaires.

En d'autres termes la réserve endothéliale qui tapisse le cœur droit constitue une ressource physiologique utilisable dans le traitement des chocs cardiogéniques.

La mise en jeu d'un endothélium pulmonaire stimulé par un petit cathéter pulsatile introduit dans le système circulatoire ouvre de nouvelles perspectives thérapeutiques pour les maladies cardiaques ischémiques et l'hypertension artérielle pulmonaire (HTAP).

Une diminution significative des résistances vasculaires pulmonaires constitue l'élément clé de l'amélioration observée de l'hémodynamique des patients. Elle est le résultat de la stimulation pulsatile de l'endothélium vasculaire des lits vasculaires splanchnique hépatique et pulmonaire, indépendamment de la fréquence cardiaque.

Au niveau du circuit du cœur droit, la validation de l'idée d'une combinaison pulsatile réalisée chez des sujets volontaires ouvre de nouvelles perspectives dans le traitement des pathologies en rapport avec de nombreux aspects de l'altération de la fonction endothéliale.

Les indications de cette nouvelle approche thérapeutique peuvent être systématisées selon les situations suivantes :

- Indication de type A, chez les patients présentant une dysfonction endothéliale associée à une pathologie cardiaque.
- Indication de type B, chez les patients présentant un cœur sans dysfonction majeure (diabète, hypertension artérielle systémique ou pulmonaire, dysfonction érectile….).
- Indication de type C, prophylactique chez des sujets sains (astronautes amenés à être soumis à des contraintes physiques conduisant à une dysfonction endothéliale) ou plus simplement dans le cadre d'une stimulation hémodynamique non spécifique au cours d'un programme de préparation des athlètes de haut niveau, ou encore dans le cadre d'un traitement anti âge.

L'utilisation d'un masque pulsatile permet d'améliorer la circulation cérébrale par une action centrale directe sur la circulation caverneuse ou par une action plus périphérique sur le système veineux jugulaire. On a pu montrer de cette façon une augmentation du débit de l'artère rétinienne en rapport avec une augmentation de son diamètre.

Ces effets permettent d'envisager l'utilisation de cette technique dans les maladies vasculaires neurodégénératives ou au décours d'un accident vasculaire cérébral. Il faut remarquer par ailleurs que ces améliorations vasculaires sont observées à distance de la zone de stimulation pulsatile c'est à dire au delà de l'endroit où est placé le dispositif (combinaison ou masque). Ainsi par exemple lors de la mise en œuvre d'un pantalon pulsatile on peut observer une nette amélioration de la microcirculation au niveau des pulpes digitales.

Au niveau du circuit du cœur gauche, on peut également augmenter les forces de cisaillement exercées par le flux circulatoire sur l'endothélium tapissant ces cavités en utilisant un tube pulsatile. Le tube pulsatile peut s'adapter dans un circuit de CEC ou d'assistance cardiaque où il permet d'obtenir des profils de pression pratiquement physiologique avec de faibles pertes d'énergie cinétique en particulier quand on l'utilise avec le canule « Smartcan». Par ailleurs il réduit considérablement la distance entre la source d'assistance cardiaque et la cible artérielle (Z3).

De la même façon, sur un modèle d'ischémie cardiaque obtenu par ligature permanente de l'artère coronaire interventriculaire antérieure gauche (IVA), l'augmentation des forces de cisaillement produite par la mise en place du cathéter pulsatile en amont du lit vasculaire pulmonaire (élément central de régulation du circuit droit) permet d'observer une amélioration de la microcirculation myocardique.

Du fait de sa demi-vie très courte mais aussi du fait qu'il est très rapidement neutralisé par l'hémoglobine, l'oxyde nitrique (NO) produit par l'endothélium ne peut avoir qu'un effet local sans action sur le lit vasculaire d'aval. C'est pourquoi il a été proposé que d'autres facteurs d'origine endothéliale, encore inconnus, puissent être impliqués dans la régulation de la microcirculation.

Les dispositifs et la méthodologie que nous proposons constituent donc un outil intéressant d'exploration de ces nouvelles voies.

Une assistance cardiaque doit prioritairement s'adresser au cœur droit. Il est en effet connu que le cœur droit « domine » le cœur gauche et ceci du fait du rôle régulateur central des résistances vasculaires pulmonaires dans le contrôle de l'hémodynamique cardiaque.

Notre méthode permet de restaurer progressivement une fonction endothéliale en maintenant des forces de cisaillement pratiquement physiologiques sur le revêtement endovasculaire. Ceci permettra d'obtenir une amélioration de la fonction myocardique évitant ainsi d'avoir recours à un arsenal thérapeutique plus radical comme la transplantation cardiaque.

De la même façon, en milieu hospitalier, le cathéter pulsatile peut être mis en place dans le tronc de l'artère pulmonaire en utilisant une voie veineuse centrale et être piloté par un petit boîtier de contrôle portable.

Les patients ainsi équipés peuvent donc bénéficier d'une stimulation pulsatile de la circulation pulmonaire sous le contrôle en temps réel de leurs paramètres hémodynamiques et ceci dans des conditions économiquement rentables.

Enfin si notre dispositif a pu montrer son efficacité thérapeutique il reste néanmoins quelques problèmes à résoudre. En particulier la stimulation directe de l'endothélium vasculaire pulmonaire ou encore des cavités cardiaques gauches en cas d'assistance ventriculaire gauche provoque des vasodilatations importantes.

Il est intéressant de remarquer que le tube pulsatile utilisé seul pour une assistance ventriculaire gauche sans mettre en œuvre la pompe d'assistance provoque une vasodilatation majeure associée à une très importante amélioration de la zone ischémique.

Ceci met en évidence le caractère extrêmement sensible de l'endothélium pulmonaire ou du revêtement endocardiaque qui donnent une réponse très rapide à une stimulation pulsatile asynchrone.

Un phénomène du même ordre a pu être observé lors de l'utilisation du Nicorandil@ dans le traitement de l'angine de poitrine.

Il faut néanmoins remarquer que ces vasodilatations majeures induites par les donneurs exogènes de NO peuvent conduire à des chocs cardiogéniques hypovolémiques. Quoi qu'il en soit, l'étude de ces hypovolémies montre qu'elles sont toujours précédées d'une amélioration générale de l'hémodynamique ainsi que de la microcirculation des organes.

Ceci se traduit par une augmentation de l'élimination hydrique rénale comme en témoigne l'apparition d'un globe vésical spontanément résolutif dans le groupe pulsatile, tandis que ces pertes liquidiennes peuvent être compensées par voie veineuse.

En pratique nous réduisons la durée des stimulations pulsatiles (5-10 minutes) elles même entrecoupées de périodes de pose définies en fonction de l'hémodynamique et plus spécifiquement par le suivi de la pression artérielle systémique.

En revanche nous n'avons pas observé de phénomènes de vasodilatation paroxystique au cours de l'utilisation des dispositifs de stimulation pulsatile externe (pantalon ou masque). Toutefois par précaution, étant donné que l'amélioration de la microcirculation se stabilise après 15 à 20 minutes de stimulation pulsatile externe, nous recommandons une durée d'utilisation du pantalon pulsatile de 20 à 30 minutes.

En outre il n'est pas nécessaire de travailler avec un régime de pression élevé car en effet un générateur de basse pression est largement suffisant pour obtenir une stimulation efficace de l'endothélium de la microcirculation cutanée superficielle.

La combinaison pulsatile étant un dispositif médical externe présente peu de contre-indications. Son usage n'est pas recommandé chez les patients cirrhotiques, chez des sujets présentant un syndrome malin (maladie cancéreuse), des fractures ouvertes, des brûlures étendues, ou encore porteur d'une colostomie ou encore au décours d'un accident vasculaire cérébrale. En tout état de cause le clinicien posera l'indication d'utilisation du dispositif selon le tableau clinique particulier à chaque patient.

Actuellement les essais cliniques utilisant ces dispositifs non invasifs sont sur le point de commencer chez des patients présentant une dysfonction endothéliale de type B (hypertension artérielle) ainsi que chez des sujets sains (type C) athlètes.

Conclusion

La nouvelle approche thérapeutique que nous proposons dans le traitement des pathologies cardio-pulmonaires et circulatoires présente l'avantage d'être plus physiologique que les approches classiques tout en restant économiquement viable.
Il s'agit d'applications cliniques, mettant en jeu un dispositif d'amplification des forces de cisaillement circulatoire (cathéter), un dispositif de restauration des forces de cisaillement (tube) et enfin un système externe d'amplification de débit et de forces de cisaillement (combinaison). En cas de défaillance cardiaque une synchronisation du dispositif avec le cœur ne s'avère pas indispensable.

Les performances de ces différents dispositifs pourront être optimisées par modélisation mathématique et détermination précise des énergies cinétiques générées par le système en fonction de la surface corporelle et des autres variables comme le choix et les emplacements des dispositifs sur les zones à stimuler.

Part III

Publications

Chapitre VII

Publications: Tube Pulsatile

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Cardiovascular Perfusion Systems: To pulse or not to pulse? Here's the answer

Short title: Pulsatile versus conventional CAD.

Authors: Sayed Nour[1,2], Jia Liu[2], Gang Dai[2], Daniel Carbognani[1], Daya Yang[2], Guifu Wu[2], Juan Carlos Chachques[1] and Qinmei Wang[2]

1- Laboratory of Biosurgical Research (Alain Carpentier Foundation), Pompidou Hospital, University Paris Descartes, Paris, France.
2- Division of Cardiology and the Key Laboratory on Assisted Circulation, Ministry of Health of China, The First Affiliated Hospital of Sun Yat-sen University, 510080 Guangzhou, China.

Corresponding author:
Dr. Sayed Nour, Laboratory of Biosurgical Research (Alain Carpentier Foundation), Pompidou Hospital, University Paris Descartes, 56 rue Leblanc, 75015 Paris, France.
E-mail: nourmd@mac.com.

ABSTRACT

Cardiac assist devices (CAD) cause endothelial dysfunction with considerable morbidity. Employment of pulsatile CAD remains controversial due to inadequate perfusion curves and costs. Alternatively, we aimed to maintain endothelial shear stress (ESS) during conventional CAD with a pulsatile tube device.

Ex-Vivo Studies: Tube was positioned in three pediatric mock circuits (I, II, III; ¼-inch), composed of conventional roller pump, oxygenator, arterial filter, aortic cannula, simulated resistance and primed with blood, at: 6 cm, 150 cm from aortic cannula, and pre-oxygenator, respectively. With various pump flow (400-1000 mL/min) and fixed pulsation (110 bpm), pulsatile and nonpulsatile flows were evaluated from pre/post: oxygenator, tube, aortic cannula and simulated resistance pressures sites. Mean pulsatile flow was significantly better than nonpulsatile in all circuits. Significant pressure losses were increased in circuits III and II compared with I. Pulse pressure was significantly increased with circuit I (126,3±18,6) compared with circuits II (66 ± 6,1) and III (48,8 ± 4,7) respectively (mmHg, $p<0.001$).

In-Vivo Studies: Prototype was connected to conventional left ventricular assist device (LVAD) in ten piglets divided into pulsatile group (P, n:5) versus nonpulsatile (NP; n=5). After ligation of the left anterior descending coronary artery and once hemodynamics deteriorated, treatment started for 2 h period, in both groups. Significant improvement of hemodynamics with clearance of ischemic zone were observed in P versus NP groups: cardiac output was 0.67 ±0.26 vs. 0.38±0.03 (L/min; $p>0.05$); systemic vascular resistances were 451.72±24.01 vs. 1309.88±151.93 (dynes.s.cm^{-5}/kg^{-1}; $p<0.001$).

In conclusion, association of a pulsatile tube device with conventional CAD could maintain ESS and improve hemodynamic with lower energy losses. This represents a cost-effective method and promotes low mortality and morbidity.

Keywords: Shear stress - Endothelial function - Momentum energy losses - Pulsatile CAD.

INTRODUCTION

Mechanical cardiac assist devices (CAD) disturb endothelial function and hemodynamics [1,2]. These most probably occur as a consequence of steady-flow or inadequate pulsatile mode of perfusion that suppresses endothelial shear stress (ESS) [3].

Shear stress-mediated endothelial function controls vascular tone with plenty of mediators [4,5], as well as vascular conditions through several processes like atherosclerosis and angiogenesis-apoptosis interdependency [6,7].

In general, the present arts of CAD can be identified in two categories: *devices* that increase coronary blood flow during diastole, in order to improve the oxygenation and thus the performance of the myocardium, i.e., the intra-aortic balloon pump (IABP), and the enhanced external counterpulsation pump (EECP) [8,9]. These devices must be synchronized with heartbeat and unsuitable in case of cardiac arrhythmia; and *devices* that unload and bypass the heart pump: either partially as achieved by left ventricular assist devices (LVAD), right ventricular assist devices (RVAD), and by extracorporeal membrane oxygenation (ECMO); or completely like with biventricular assist devices, extracorporeal circulation (CPB) [10-12].

Conceptually, these devices are lumped models, designed for driving Newtonian compressible fluids inside closed pressurized hydraulic circuits implementing rigid tubes with fixed diameters [13, 14]. Meanwhile, in practices those devices are confronted with blood, which is a non-Newtonian fluid running inside flexible vessels with different geometries and controlled by vascular resistance. Thus, confrontation between these two opposite pressurized hydraulic circuits creates a vicious circle of momentum energy losses and endothelial dysfunction. Besides, installations conduits between cardiovascular tissues and CAD create dead space with important zones of energy losses (15).

Finally, permanent replacement of the heart with an artificial heart option is still a work in progress with short life expectancy, which limits its applications in specific categories, regarding body surface area (1.9 ± 0.22 m^2), sex (95% men) and age (practically 0% children) [16,17].

In a matter to overrule these side effects, different therapeutic strategies are currently applied, particularly with CPB such as: *pharmacological supports* [18]; *normothermia* [19]; and *pulsatile* CPB [20]. However, those trials remain insufficient, as drugs promote further drawbacks [21]. Benefits of normothermia that may be due

to the stability of blood viscosity at 37°C [22], remain controversial [23], as the myocardium is already protected with cardioplegia. In addition, perfusion of organs microcirculation is protected with hemodilution according to the Fahraeus-Lindqvist effect [24]. Besides, current pulsatile CPB induce inadequate perfusion curves and momentum energy losses that necessitate specific materials and technology [25]. On the other hand, association of IABP with conventional CPB, as a cost-effective manner creates turbulent zones from opposing flows and vascular complications [26-28].

These side effects may explain current popularity of conventional CPB [29], in addition to the *off-bypass technique*, which is still restricted to small groups of patients [30].

Therefore, an optimum cardiovascular perfusion device is till missing, because we cannot simulate properly a type-III passive ventricular pump with type-I (e.g., roller), or type-II (e.g., centrifugal) pumps [31,32].

Alternatively, we are proposing a new concept of pulsatile CAD based on a fundamental revision of the entire circulatory system in correspondence to the physiopathology and law of physics.

As shown in (Figure 1 A), it concerns a double lumen disposable tube device that could be adapted to conventional CPB and/or CAD, for inducing a homogenous, downstream pulsatile perfusion mode with lower energy losses.

In this study, device prototypes were tested in a simulated conventional pediatric CPB circuit for energy losses and as a LVAD in ischemic piglets model for ESS evaluations.

The goals of this study were to evaluate the feasibility of the proposed device to transform a steady-flow of conventional CAD into a pulsatile mode of perfusion with preservation of physiological ESS and minimum energy losses. This represents a cost effective method with low morbidity and mortality.

Materials and Methods

Device prototype

A double lumen tube (Figure 1 B), composed of: a) external polyvinyl chloride (PVC) (20 cm length, ½ inch diameter). b) Internal Polytetrafluoroethylene (PTFE) (18 cm length, 12mm diameter) reinforced with latex membrane (condom), to avoid any leakage through PTFE micropores. c) 2 connectors (¼ inch) were introduced at each end of the inner tube and securely sealed by external adhesive straps and rings in a wedged manner to the external PVC tube. A small animal ventilator (HX-300 TaiMeng Technologies Inc®) was connected to the intermediate chamber through central holes at the external tube to be used as a pulsatile generator.

1.1. In vitro study

Mock circulation

With slight modification, according to Undar et al; Wang, et al. [33, 34], the circuit was composed of (Figure 2 A): a roller head pump (Cobe® Cardiovascular Inc.), pediatric oxygenator (Sorin® Lilipput 2 Ecmo) and hemofilter (Sorin® Group hemoconcentrators), primed with fresh piglet's blood mixed with dextrane in concentration of: 2/3-to-1/3, respectively. A pediatric arterial line circuit, PVC tube (1.5 m length), 14 FR aortic cannula (DLP® Medtronic, Inc.), venous line (1.5 m length) and simulating vascular resistance partial clamp, positioned downstream to the aortic cannula.

Methods

Five pressure lines were connected to a pressure monitor (BIOPAC® physiology monitoring system) and positioned at remote spots on the circuit as follows: *pre/post* oxygenator (P1, P2); *pre/post* tube (P3, P4) and *post* simulated resistance (P5), which represents the arterial perfusion curve in patients (Figure 2 B).

Flow-pressure curves were recorded first in a steady mode, then pulsatile after switching the tube's generator on, using variant pump flow rate (400, 600, 800 and1000 mL/min) and fixed pulsatile frequency (110 bpm) in group P.

Momentum energy losses were roughly calculated according to differences of flow pressures between the spots (P1-P5) and compared with tube position in 3 different mock circuits as following:

- Circuit I: the tube was positioned downstream to the oxygenator at 6 cm distance from the aortic cannula.

- Circuit II: the tube was positioned downstream to the oxygenator at 150 cm distance from the aortic cannula.
- Circuit III: the tube was positioned upstream between the roller pump and oxygenator.

1.2. In vivo study:

This study was approved by the Animal Research Facility at Sun Yat-Sen University and conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No.85-23, Revised in 1996).

Ten domestic piglets of both sexes were randomly designated to either pulsatile group (P, n=5; 11.75±0.60 kg) or the non-pulsatile group (NP, n=5; 11.80±0.84 kg). Animals were premedicated and maintained on general anesthesia according to our previously published protocols [35]. After a median cervicotomy and tracheotomy, a 3.5 - 5 # tracheal tube was inserted, followed by mechanical ventilation (PA-500 PuLang Technologies Inc®) with 40% oxygen, 10-15 ml/kg/min of tidal volume and frequency of 15/min. The right carotid artery was isolated and cannulated with a 6 Fr. arterial sheath. Then a Millar probe (4 Fr. MIKRO-TIP® catheter transducer, Millar Instruments) was introduced through the carotid line into the aorta for continuous systemic pressure (AP) monitoring (BIOPAC® physiology monitoring system); this enabled other hemodynamic measurements mentioned below. After median sternotomy, mediastinal dissection, pericardiotomy, and dissection of great vessels followed by positions of purse-string (5/0 *polypropylene)* at the RA appendage, infundibulum, ascending aorta and LV apex.

Cardiac catheterizations / Hemodynamic monitoring: A (5 Fr.) double-lumen central venous line (Hydrocath™, B-D Tech.) was introduced through the RA purse-string for drug administration and RA pressure monitoring. An intrapulmonary catheter (5 Fr. Swan-Ganz®) was introduced through the infundibular purse-string for pulmonary artery pressure (PAP). Left atrium (LA) pressure was obtained by direct needle puncture at pre-determined time points. Cardiac output (CO) was measured with a TRANSONIC® transit-time flowmeter temporarily positioned around the aortic root at pre-determined time points.

Total time (T) of the experiment was 3 h, divided into (T1, T2, T3) in correspondence to data collection: T1**=** baseline; T2= nearly I h of myocardial ischemia, just before

severe hemodynamic deterioration; and T3 = by the end of experiment after 2 h of treatment.

Induction of acute myocardial ischemia: After surgical preparation, and data collection for T1, the left anterior descending coronary artery (LAD) was encircled with a 4/0 polypropylene stitch, distal to the 2nd diagonal bifurcation and tightly obstructed with a snugger for 2 h period.

During the first 1 h of ischemia, ventricular fibrillation (VF) and cardiac arrest were frequent after 20-30 min of ischemia. Animals were assisted with classical cardiopulmonary resuscitation (CPR) and DC shocks (20-30 J), without any further IHD pharmacological supports.

After 30 min, heparin was given (250UI/kg) intravenously, followed by LVAD installation as follows:

In P group, a modified aortic cannula (12 Fr., 10 cm length; DLP®-Medtronic, Inc.) was inserted at the aortic root and a short piece of PVC tube (14 Fr., 15 cm length) was introduced into the LV apex. Both aortic cannula and LV vent were shortly cut in a matter to avoid energy losses caused by unnecessary length. A pulsatile tube prototype was connected at its distal end to a conventional roller pump (Cobe® Cardiovascular Inc.) and to the aortic cannula at its proximal end. The LV vent was connected to the other end of the roller pump.

In NP group, the aorta was cannulated using a standard aortic cannula (12 Fr. DLP®-Medtronic, Inc.) and an apical LV vent (14 Fr. DLP®-Medtronic, Inc.). Both aortic and LV vent were connected to a centrifugal pump (Sorin group Revolution ®).

The LVAD circuit in both P and NP groups was primed with heparinized saline, then been de-aired, clamped and kept on standby until T2. Animals that did not survive T2 were excluded.

Hemodynamics data were collected from both groups at T1, T2 and T3 including: AP, PAP, LA, and RA pressures, heart rate and CO. The vascular resistance index was calculated with the flowing formula:

Pulmonary vascular resistance index (PVRI) = 80* (MPAP – PCWP) / CO*Wt

Systemic vascular resistance index (SVRI) = 80* (MAP – CVP) / CO*Wt

Where: MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure, substituted for LA pressure; MAP = mean arterial pressure; CVP = central venous pressure, substituted for RA pressure; CO = cardiac output; and Wt = body weight.

Therapeutic phase: During the second hour of ischemia in P group, the pulsatile tube generator was switched on at a fixed frequency (90 bpm) and irrespective of heart rate (93.75±5.25 bpm). The flow rate of the roller pump was kept around 0.3L/min (150ml/Kg). In the NP group, the centrifugal pump flow rate was fixed around 0.8 L/min.

After 1 h of LV mechanical assist, the LAD snugger was released, allowing coronary reperfusion during the second hour of assistance (total 2 h of LVAD).

The ischemic zone was measured and evaluated macroscopically until the end of the experiment (T3).

Animals were euthanized with a 10 ml injection of saturated potassium chloride (KCl) upon completion of 3 h of LVAD, or just before severe hemodynamic deterioration.

Statistics: Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test hemodynamic data in vitro and a 2-way ANOVA for the in vivo data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

Results:

***In vitro*,** as been resumed in (Table 1) and (Figures: 3-5): globally, mean flow pressures at P5 were significantly, better in the pulsatile mode (P) compared with steady flow (NP): mean P5 were 31,8 ± 1 versus 30,8 ± 0,5; 40,3 ± 0,5 versus 39,3 ± 0,5; and 44,8 ± 0,5 versus 43 ± 0,00 mmHg with tube position in circuits I, II and III, respectively ($p<0.001$).

Reduction of the pulsatile perfusion curve amplitude was directly proportional to distance between aortic cannula and tube position, i.e. I > II > III.

The collected pulse pressure data from each circuit were:

Circuit I = P4 (133,3 ± 17,7) - P5 (126,3±18,6) ≈ 7 mmHg.

Circuit II = P3 (100,3 ± 10,3) - P5 (66 ± 6,1) ≈ 44 mmHg.

Circuit III = P2 (74,5 ± 8,7) - P5 (48,8 ± 4,7) ≈ 26 mmHg. In circuit III, there were significant increased flow pressures in a retrograde manner i.e. P1 > P2 and P5 > P1 ($p<0.001$).

In vivo, as been resumed on (Table 2): Apparently, the induced pulsatile perfusion curve was nearly physiological in amplitude as shown on (Figure 6 A). Clearance of the ischemic zone with better hemodynamic were observed in group P compared with the NP group (Figure 3 B). In P group heart rate was 76.25±5.12 versus 99.25±3.77 in NP (bpm; $p<0.05$). Hemodynamic (Figure 3 C) was better in the P group compared with NP. Cardiac output (CO) was *nonsignificantly*, increased in the P group compared with NP: CO was 0.67 ± 0.26 versus 0.38±0.03 (L/min; $p>0.05$), respectively. There was significant vasodilatation in the P group compared with NP: Mean AP in the P group was 46.83±0.52 versus 79.88±1.65 in NP group (mmHg; $p>0.05$); Mean PAP in P was 24.83±2.88 versus 34.53±7.68 in NP group (mmHg; $p>0.05$); SVRI was 451.72±24.01 versus 1309.88±151.93; and PVRI was 210.66±16.02 versus 566.98±97.98 (dynes.s.cm^{-5}/kg^{-1}; $p< 0.001$), respectively.

Operative movies for both the in vitro and in vivo studies are available on the following site: www.nourmd.com.

Discussion

In this study, conventional steady-flows of a simulated CPB circuit, and LVAD were transformed successfully, into a pulsatile mode of perfusion, using a double lumens tube device.

In vitro, there were significant pressure losses with tube position in circuits III and II compared with, I. In vivo, the induced pulsatile perfusion curve was efficient to improve hemodynamic and restore endothelial function in the P group compared with NP group.

Normally, fluid movement in hydraulic circuits, which means momentum transfers with frictional losses, depends on driving forces, resistances, viscosity and conduits geometries [36].

Nevertheless, quantifications of lumped models that could be achieved with accuracy according to the Bernoulli's principles of energy losses in vitro remain controversial due to different cardiovascular criteria [37,38].

Endothelial shear stress (ESS) that control vascular resistances, could be influenced by hemorrheological changes, particularly, pulse pressure and/or shear rate [39,40].

For example, under normal hemorheological conditions, microcirculation behavior approaches that of Newton's second law, such as seen in athletics, i.e., a high physical performance (ESS) can be induced by increasing the pulse pressure and slowing the heart rate (shear rate). In contrast, in any abnormal hemorheological state, microcirculation presents behavior that approaches that of Bernoulli's 3rd equation, which is interpreted by the Fahraeus-Lindqvist effect [24], in which plasma becomes stuck at the inner vascular boundary layers, whereas erythrocytes move faster at the center [35]. These may explain clubbing fingers phenomena in cyanotic heart disease.

Therefore, delivery of ESS with pulsatile CAD should be induced according to the biophysics and pathophysiological conditions of each heart circuit (Figure 7).

Physiologically, the left heart side has specific morphological particularities that must be considered.

The left ventricle (LV) and peristaltic arteries represent the main circulatory driving forces at the left heart circuit, which deliver almost constant shear rate and pulse pressure. Flow dynamics inside the Valsalva sinuses determines coronary ostia morphogenesis [41], and may contribute to a severe hemodynamic

deterioration [42]. This means delivery of ESS with CAD must be induced at the left heart side according to Newton's law by maintaining adequate pulse pressure.

Contrarily to the left heart side, the right heart side can adjust blood volume and shear rates at five different anatomical zones according to its physiological demands [43]. The PA represents a low-level remodeling zone, similar to systemic veins. At the same time, PA compliance is much greater than that of the large veins [44]. Therefore, direct induction of shear stress according to Newton's law, using intravenous (IV) or intrapulmonary pulsatile CAD, must be avoided at the right heart side. Most importantly, delivery of ESS should not disturb the physiological remodeling of the right heart circuit because increased ESS with high pulse pressure promotes serious hemodynamic conditions and irreversible remodeling, such as Eisenmenger syndrome [45]. In addition, the RV is preload dependant that could not tolerate to be unloaded [46].

These may explain, insufficiency of current CAD employments in congestive heart (CHF) patients with severe RV failure that still exhibit a high mortality rate (65%-95%) [47]. In pediatrics, applications of CAD remain controversial, as most of were designed for management cardiovascular diseases (CVD), in adults, and then miniaturized to cope with pediatric populations. However, pediatric patients are more vulnerable to hemodynamic disturbances caused by right heart failure due to congenital anomalies versus adults CVD most commonly caused by left ventricular ischemia and atherosclerosis [48].

The proposed pulsatile tube device adapts biophysics and pathophysiological conditions of the *left heart*. This promotes pulsatile tube applications with conventional CPB and LVAD or as biventricular-assist device in association with a pulsatile suit device for a right ventricular-assist device [46].

Practically, and for better understanding of the pulsatile tube's function as a cardiovascular perfusion device, we propose a state of momentum energy losses that could be identified in 6 main zones (Figure 8), as follows: pre/post oxygenator (Z0, Z1), tube zone (Z2), post-tube *or* pre-aortic cannula (Z3), aortic cannula (Z4) and cardiovascular system (Z5).

Normally, pulsatile tube (Z2), receives steady-flow from Z1, then the propagated pulsatile impacts move the stagnant blood boundaries' layers at the inner flexible tube and push them towards the center according to the "Bernoulli" principles. These would promote fewer traumatic effects of blood components compared with

current devices. In addition, the downstream position of the pulsatile tube, which avoids already two obstructive zones of energy losses, makes high cost accessories unnecessary [49,50]

The present study results showed the importance of energy losses in correlation to circuits length. Particularly, the distance between the pulsatile tube and the pre-aortic cannula (Z3), which was represented by P4 in position (I), P3 and P2 in positions II and III, respectively. Eventually, these constitutions of vortices in Z3 are the consequences of strong pulsatile impacts inside rigid tubes with fixed geometries. Thus, compromising this Z3 distance between patients and CAD is crucial.

In contrast, energy losses were very important with tube position in circuit III, which simulates current pulsatile CPB and/or CAD. We have observed severe leakage after few minutes of pulsations (≤ 5 min) with circuit III. The increased pressure at P5 due to this retrograde turbulent flow was enhanced by the application of a non-occlusive pump (Table 1). In addition, the pulsatile tube became an obstructive zone per-se in positions II and III.

Energy losses inside the aortic cannula (Z4) are usually, caused by unnecessary length and tapering end. We have attempted to diminish these drawbacks of unnecessary length by shortening the aortic cannula in the P group.

At the cardiovascular side (Z5), turbulent flow of energy losses that starts from the tip of aortic cannula (divergent diffuser) will be absorbed by the arterial wall filter to be dependent on ESS that control organs microcirculations [51].

According to the present study results, the induced pulsatile tube pulse pressure of the (Figure 6A), improved hemodynamic with almost complete clearance of the ischemic zone after few minutes of pulsatile flow assistance in the group P compared with NP.

Contrarily to the NP group, the induced vasodilatation of the pulsatile group was most probably caused by endothelial vasodilators secretion (e.g. NO), which means maintenance of ESS with tube pulsations. By the end of the experiment (T3), heart rate was 76.25±5.12 bpm in group P compared with 99.25±3.77 bpm in the group NP, which signifies better hemodynamics with less myocardial oxygen consumption.

In addition, myocardial recoveries in the pulsatile group occurred in pediatric immature myocardium of animal model with poor collaterals [52,53, which intensify the role of subendocardial microcirculation [54].

We should emphasize that in all our in vivo studies, the tube pulsations were not synchronized with heart rate. This confirms our therapeutic policy based on similar observations with other pulsatile devices (e.g., suit and catheter), proving that pulsatile CAD should not be synchronized with the heartbeat in case of heart failure [15].

Interestingly, the pulsatile tube was tested as a stimulator of the LV subendocardium without association roller pump, in *two* ischemic piglets (please refer to operative movie: www.nourmd.com). There was rapid clearance of the ischemic zone and improved contractility, after few minutes of unsynchronized pulsations (110 bpm; ≤ 5min), followed by severe vasodilatation.

This proved the hypersensitivity of the LV endocardium and heterogeneity of the left heart endothelium that may be an emerging concept regarding the endothelial impact of current devices [55, 56].

Study Limitations

Although these results proved that pulsatile tube was efficient to maintain ESS, some weak points must be improved. This includes microporosity of the inner tube (PTFE), which became almost collapsed by the external latex membrane cover. Accordingly, tube association with a hypersensitive sophisticated centrifugal pump was impossible. There were centrifugal pump failures in two excluded piglets from the NP group due to uncontrolled systemic hypertensive crises (≥140 mmHg). Therefore, the use of a non-occlusive roller pump increased the circuits' artifacts, particularly III and II, and disturbed the applications of more recent formulae for energy losses evaluations [33,34]. In addition, latex did not stop impregnations of the inner tube with blood that made homogenous histopathological and biological data very doubtful.

Improvements

The proposed study concept deserves further evaluations with more enlarged investigations. To overcome the current limits, we are developing a new device with an inner tube made of (ChronoFelx® AR), which is similar to PTFE hardness (65A-75A) but without micropors. These enabled us to continue our ongoing studies: a) pulsatile versus non pulsatile LVAD in ischemic piglet models; b) biventricular assist device combining the pulsatile tube as a LVAD and the pulsatile trouser as right

ventricular assist device (RVAD) [45]. We are planning a new animal model for evaluating the effectiveness pulsatile tube, associated with conventional CPB during the first trimester of pregnancy.

Conclusion

Pulsatile tube adaptable to conventional perfusion devices, could induce homogenous, downstream and nearly physiologic pulsatile perfusion flow, with lower energy losses. This represents a cost-effective promising method with low mortality and morbidity, especially in fragile cardiac patients.

Acknowledgements

We would like to express our gratitude for the great help of Drs. Alain Carpentier, Claude Planché, Pierre Chastanier and Michel Guinet.

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Figures legends

Figure 1 (A): Disposable pulsatile tube (pipe)

According to patents descriptions (World Intellectual Property Organization : WO/2008/000110 & WO/ 2010/066899): 1= Flexible inner tube; 2 = Rigid external tube; 3 = Intermediate chamber; 4 = Ports; 5 = Connectors.

Figure 1 (B): Pulsatile tube prototype

External polyvinyl chloride (PVC) tube (#1/2 inch); Internal Polytetrafluoroethylene (PTFE) tube (#12mm) and connectors (#1/16-1/4 inch).

Figure 2 (A): Mock-circulation: energy losses circuit (I)

1 = arterial perfusion line; 2 = pulsatile tube; 3 = aortic cannula; 4 = venous line; 5 = pressures lines; 6 = partial tube clamp (simulated resistance).

Figure 2 (B): Mock-circulations with 3 different tube positions

{I} = Pulsatile tube was positioned at *6 cm* distance from aortic cannula; {II} = Pulsatile tube positioned at *150 cm* distance from aortic cannula; {III}. Pulsatile tube wedged between roller pump and oxygenator. 1 = roller pump; 2 = oxygenator; 3 = arterial line; 4 = pulsatile tube; 5 = aortic cannula; 6 = resistance (tube clamp); 7 = venous line. P1, P2, P3, P4, P5 = perfusion pressures recording spots.

Figure 3: Perfusions curves (in vitro)

Perfusion curves (in mmHg) obtained at different circuit sites in 3 different pulsatile Tube positions: I, II, III close & distant from aortic cannula and pre-oxygenator respectively. The perfusion curve amplitude was significantly higher at P5 with position I, compared to positions II & IIII.

Figure 4: comparative steady and pulsatile flow perfusion curves obtained from 3 different circuits

Energy losses 1 (upper panel) = pulsatile tube at 6 cm from aortic cannula; Energy losses 2 = pulsatile tube at 150 cm from aortic cannula; Energy losses 3 = pre-oxygenator pulsatile tube position. P1-P5 = distant circuit spots for perfusion pressure records (mmHg). NP= non-pulsatile; Pm = mean pulsatile pressure, Ps = systolic pressure; Pd = diastolic pressure; PP = pulse pressure. The pulse pressure (green color) was significantly higher with position I compared to positions II & III.

Figure 5: Pulsatile flow pulse pressure (upper panel) and systolic pressure (lower panel8)

Energy losses with different tube positions: I = 6 cm from aortic cannula; II = 150 cm from aortic cannula; III = pre-oxygenator. P1-P5 = perfusion pressure records (mmHg) at main circuit energy losses spots. At P5 the pulse pressure (upper panel) as well as the systolic pressure (lower panel) were significantly higher in position I (red color) compared to other position II (blue color) and III (violet color)
Circuit I: P1, P2 = pre/post oxygenator pressure; P3, P4 = pre/post tube. *Circuit II*: P1 = pre-oxygenator; P2, P3 = pre/post Tube; P4 = pre-aortic cannula. *Circuit III*: P1, P2 = pre/post Tube; P3 = post-oxygenator; P4 = pre-aortic cannula. P5= post simulated resistance in all circuits. Pm = mean pulsatile pressure; Ps: systolic pulsatile pressure, Pd: pulsatile diastolic pressure; PP: pulse pressure. Pulse pressure was higher at P5 in circuit I, compared with II and III. Pm was higher at P5 compared to NP with position I. ($p<0.001$).

Figure 6 (A): Pulsatile LVAD perfusion curve in ischemic piglets

Unsynchronized pulsations with heartbeat perfusion curve with nearly physiological pulse presssure

Figure 6 (B): Pulsatile LVAD in piglet ischemic model

Left panel: shows a massive myocardial ischemic zone after LAD ligation; right panel: clearance of the ischemic zone after 15 min of pulsatile LVAD (roller pump + pulsatile tube). 1 = Aortic cannula; 2 = LAD permanent snugger; 3 = left ventricular apical vent; 4 = intrainfudibular pulmonary artery and Millar right ventricular pressure catheters; 5 = right atrium pressure line.

Figure 6 (C): Hemodynamic results of pulsatile and non-pulsatile left ventricular assist device in ischemic piglet model.

P: pulsatile group; NP: non-pulsatile group; MAP: mean arterial pressure (mmHg); CO: cardiac output (L/min); SVRI: systemic vascular resistance index (dynes.s.cm^{-5}/kg^{-1}); PVRI: pulmonary vascular resistance index (dynes.s.cm^{-5}/kg). T1: baseline; T2: 1 h of shunt; T3: 1 h after treatment.

Figure 7: Different remodeling zones (Z) of Left and right hearts circuits [(15)]

Left heart: Z1 = left ventricle pump; Z2 = peristaltic aortic pump + Valsalva

Right heart: Z1= systemic veins; Z2 = atrio-ventricular cavity; Z3 = interventricular septum; Z4 = infundibulum; Z5 = pulmonary artery.

Figure 8: Main momentum energy losses zones within a CPB perfusion circuit [(15)]

Z0 = conventional CBP (1); Z1= post-oxygenator (2) arterial line; Z2= pulsatile tube; Z3=pre-aortic cannula zone; Z4=aortic cannula; Z5= patient.

table
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Groups		P1	P2	P3	P4	P5
1 -	NP (I)	32,5 ±1,3	31,3 ± 1,3	30,3 ± 0,5	30,3 ± 0,5	30,8 ± 0,5
	NP (II)	36,3 ±1,3	37,8 ± 1	39,5 ± 0,6	38,5 ± 0,6	39,3 ± 0,5
	NP (III)	40,3 ±1	42,3 ± 1	43 ± 0,00	42,3 ± 0,6	43 ± 0,00
2 -	Pm. (I)	34,5 ± 1,7	34,5 ± 1,3	33,5 ± 1,7	32,3 ± 1	31,8 ± 1
	Pm. (II)	39,3 ± 0,5	40 ± 0,8	40,8 ± 0,6	40,5 ± 0,6	40,3 ± 0,5
	Pm. (III)	43 ± 1,2	46 ± 2,2	46,3 ± 1,5	44 ± 0,8	44,8 ± 0,5
3 -	Ps. (I)	72 ± 3,5	81 ± 11	92,8 ± 4,9	98 ± 11,5	92,8 ± 5,6
	Ps.(II)	97,3 ± 7	92,3 ± 6	90 ± 11,2	81,3 ± 7,5	82,3 ± 8,4
	Ps. (III)	84,3 ± 6,6	79,8 ± 5,9	79,8 ± 5,5	69 ± 3,9	69 ± 4,2
4 -	Pd. (I)	(-)4,4 ± 3,2	(-)6,5 ± 7,4	(-)13,6±11,7	(-)35,3±8	(-)33,5±13,3
	Pd. (II)	(-)1,1 ± 6,2	(-)7,8 ± 4,4	(-)0,8±9,4	5,6 ±8,4	13 ±3,2
	Pd. (III)	0,5 ± 10	5,3 ± 5,3	7,5 ± 7,5	20,3 ± 3,8	20,3 ± 0,5
5 -	PP (I)	76,4 ± 3,4	87,5 ± 11,8	106,4 ± 15,9	133,3 ± 17,7	126,3±18,6
	PP (II)	98,3 ± 7,9	100 ± 10,4	100,3 ± 10,3	75,7 ± 15,4	66 ± 6,1
	PP (III)	83,8 ± 9,2	74,5 ± 8,7	72,3 ± 12,6	48,8 ± 7,1	48,8 ± 4,7

Table 1: Pulsatile and non-pulsatile (NP) flows pressures records (mmHg) of three different mock circuits (I, II and III).
Circuit I: P1, P2 = pre/post oxygenator pressure; P3, P4 = pre/post tube. *Circuit II*: P1 = pre-oxygenator; P2, P3 = pre/post Tube; P4 = pre-aortic cannula. *Circuit III*: P1, P2 = pre/post Tube; P3 = post-oxygenator; P4 = pre-aortic cannula. P5= post simulated resistance in all circuits. Pm = mean pulsatile pressure; Ps: systolic pulsatile pressure, Pd: pulsatile diastolic pressure; PP: pulse pressure. Pulse pressure was higher at P5 in circuit I, compared with II and III. Pm was higher at P5 compared to NP with position I. ($p<0.001$).

`

	T1		T2		T3	
GROUPS	**P**	**NP**	**P**	**NP**	**P**	**NP**
Wt*	11.75±0.60 ‡	11.80±0.84	nd	nd	nd	nd
HR*	85.4±7.92 ‡	89.00±9	93.75±5.25 ‡	102.33±6.43	76.25±5.12 ‡	99.25±3.77
MAP*	75.66±3.1 ‡	76.6±3	71.73±9.3‡	82.35±2.16	46.83±0.52	79.88±1.65 ‡
MPAP*	24.93±5.6 ‡	27.44±7.17	38.13±5.44 ‡	41.47±1.46	24.83±2.88	34.53±7.68 ‡
LAP*	2.62±0.61 ‡	2.28±1.1	2.28±0.69 ‡	2.33±0.57	2.6±0.48	1.78±0.26 §
RAP*	2.60±0.55 ‡	3.78±1.09	4.8±2.05 ‡	5.4±2.03	2.6±1.67 ‡	3.85±0.86
CO*	0.87±0.1 ‡	0.9±0.13	0.5±0.11 ‡	0.6±0.04	0.67 ±0.26	0.38±0.03 ‡
SVRI†	600.22±45.27 ‡	610.6±112.37	1046.57±156.05 ‡	899.28±15.82	451.72±24.01	1309.88±151.93 §
PVRI†	174.93±20.95 ‡	215.71±42.93	583.02±144.93 ‡	471.38±12.58	210.66±16.02	566.98±97.98 §

Table 2: Hemodynamic results of pulsatile and non-pulsatile left ventricular assist device in ischemic piglet model.

P: pulsatile group; NP: non-pulsatile group; Wt = weight (kg); HR = heart rate (bpm); MAP: mean arterial pressure (mmHg); MPAP: mean pulmonary arterial pressure (mmHg); LAP: left atrial pressure (mmHg); RAP: right atrial pressure (mmHg); CO: cardiac output (L/min); SVRI: systemic vascular resistance index (dynes.s.cm^{-5}/kg^{-1}); PVRI: pulmonary vascular resistance index (dynes.s.cm^{-5}/kg). *measured variables; †calculated variables; ‡$P > 0.05$ between the P and NP groups; §$P < 0.05$ between the P and NP groups. T1: baseline; T2: 1 h of shunt; T3: 1 h after treatment. Group P: pulsatile tube frequency: 90 bpm; Roller pump flow 0.34± 0.02 L/min. Group NP: centrifugal pump flow = 0.80 L/min.

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Nour (pulsatile tube)

Figure 1 (A)

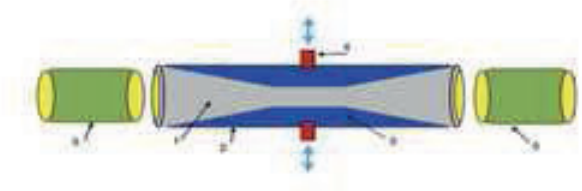

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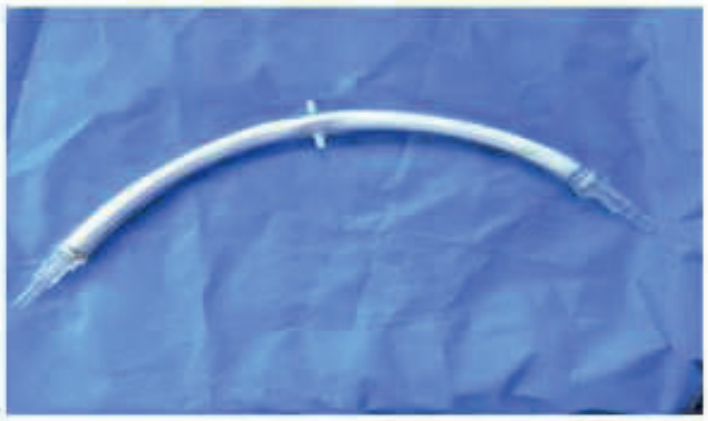
Figure 1 (B)



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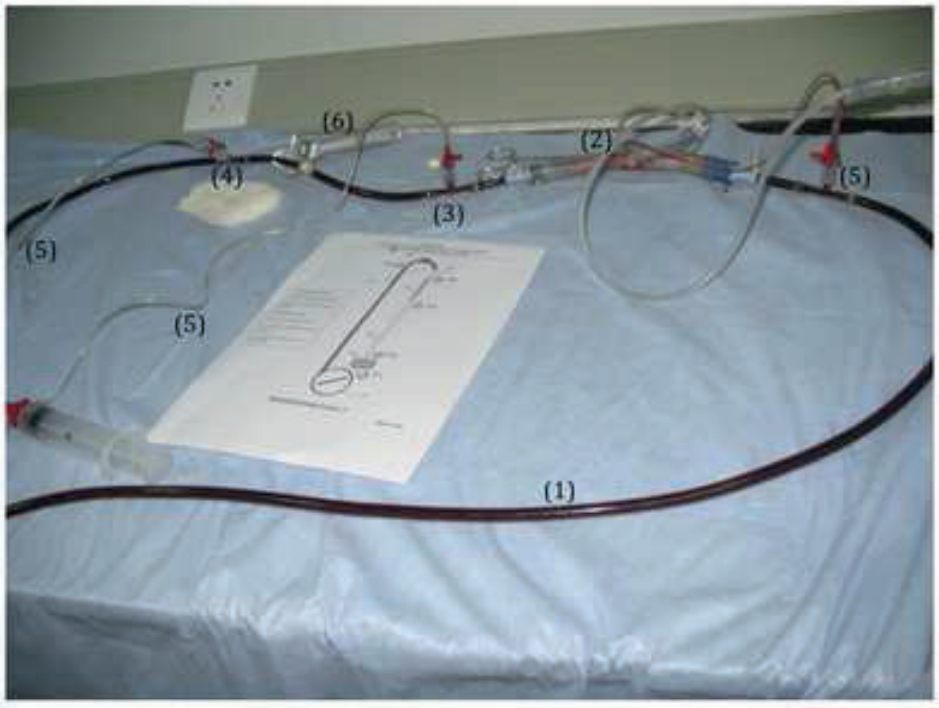
Nour (pulsatile tube)

Figure 2 (A)



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Nour (pulsatile tube)

Figure 2 (B)

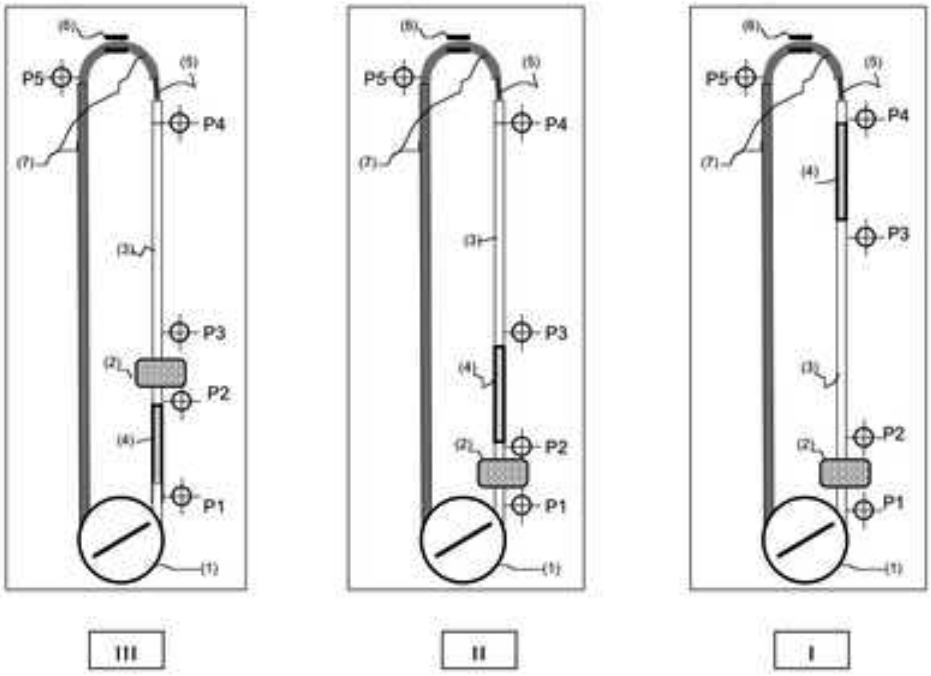

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Figure 3

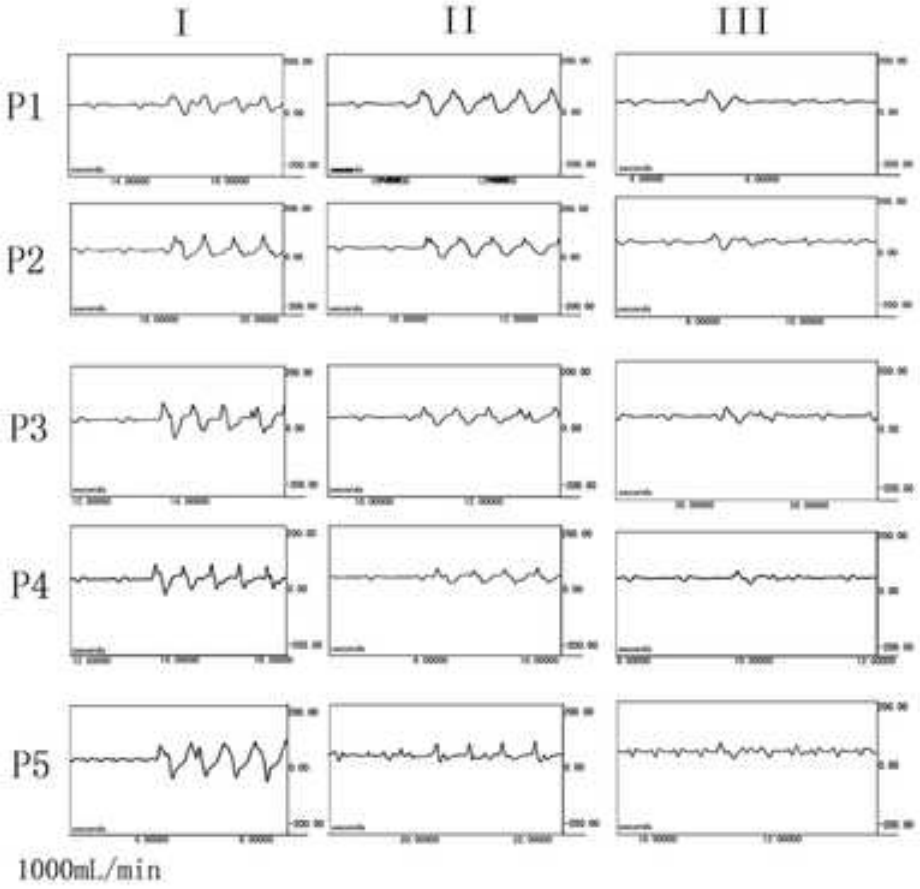

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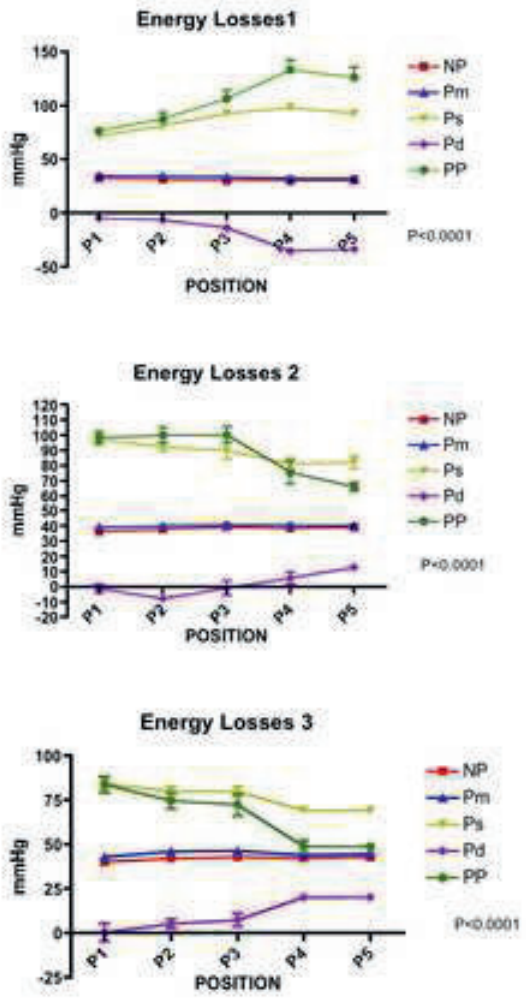
Figure 4



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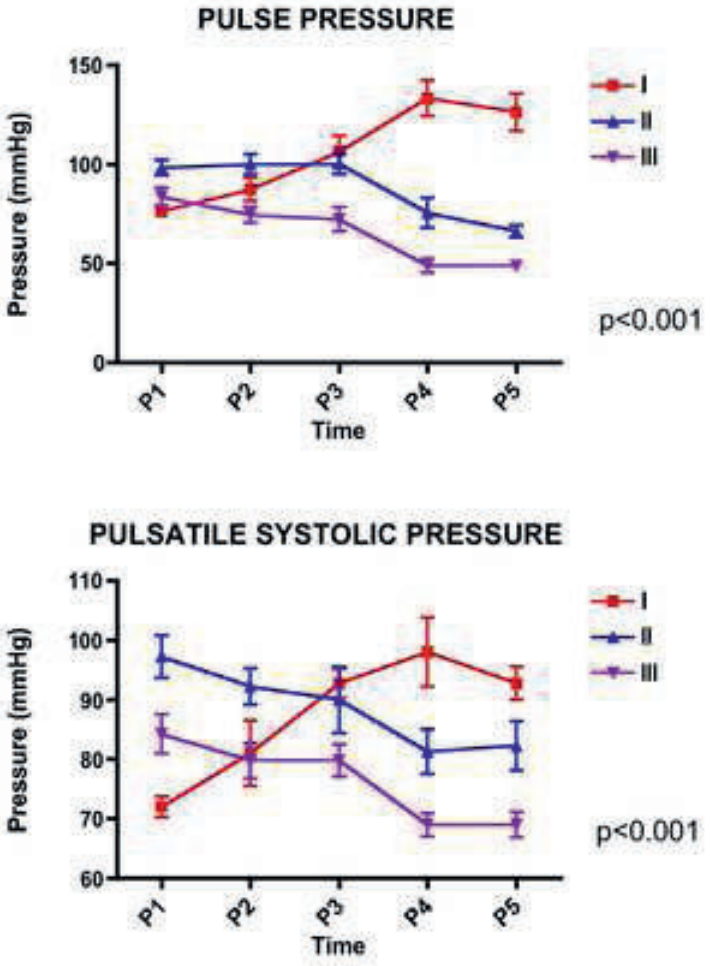
Nour (pulsatile tube)

Figure 5



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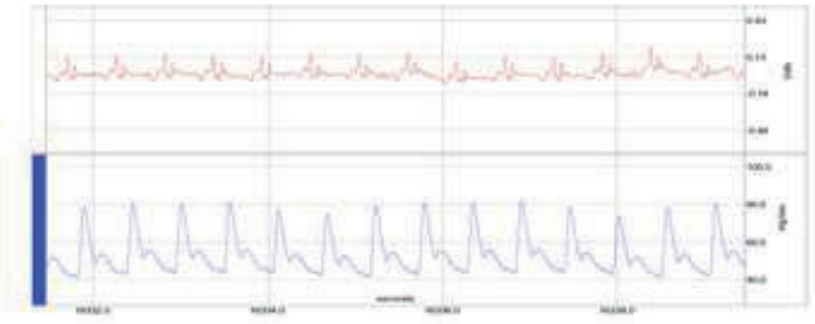
Nour (pulsatile tube)

Figure 6 (A)



colour figure
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Nour (pulsatile tube)

Figure 6 (B)

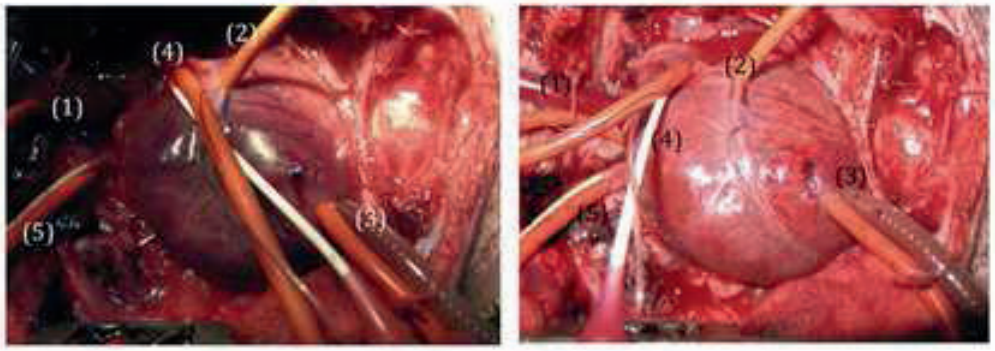

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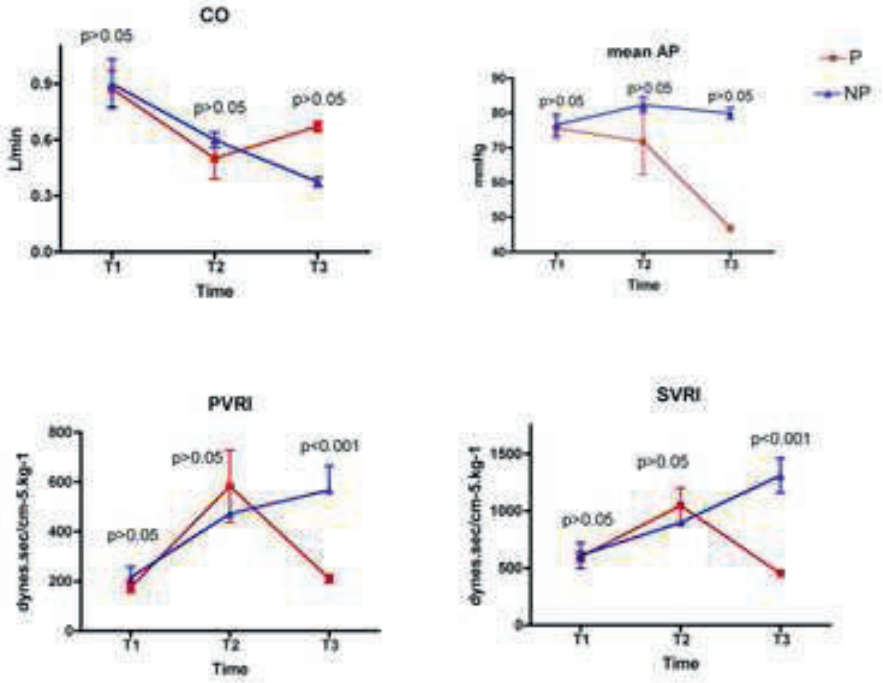
Figure 6 (C)



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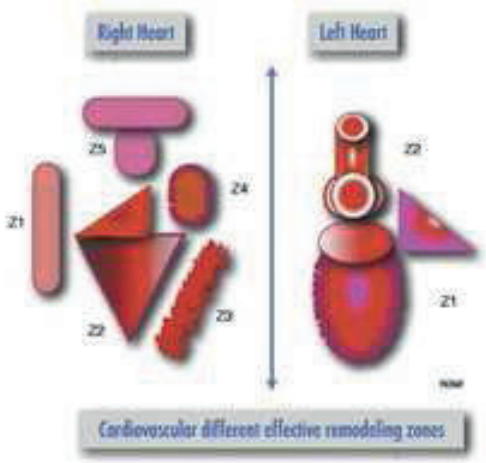
Nour (pulsatile tube)

Figure 7



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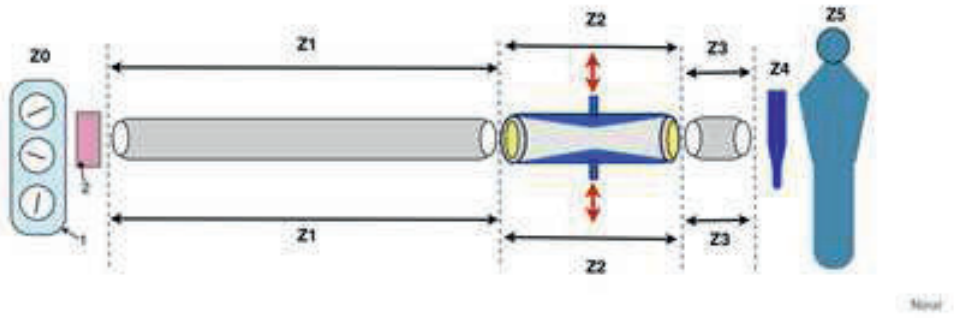
Nour (pulsatile tube)

Figure 8



Chapitre VIII

Publications: Cathéter Pulsatile

- Étude expérimentale « L'infarctus myocardique aigue »
  Soumis le 1808/2012 : Basic Research in Cardiology (pp162-197).

- Étude expérimentale « L'hypertension artérielle pulmonaire aigue »
  Publié : Pediatric Cardiology Journal (pp 198-211).

Title: Intrapulmonary shear stress enhancement: a new therapeutic approach in acute myocardial ischemia

Short title: Pulmonary shear stress in myocardial ischemia

Authors: Sayed Nour MD[1,2], Daya Yang MD[2], Gong Dai MS[2], Qinmei Wang[2], Minze Feng MS[2], Nermine Lila PhD[1], Juan Carlos Chachques MD PhD[1] and Guifu Wu, MD PhD[2]

1- Laboratory of Biosurgical Research (Alain Carpentier Foundation), Pompidou Hospital, University Paris Descartes, 75015 Paris, France.
2- Division of Cardiology and the Key Laboratory on Assisted Circulation, Ministry of Health of China, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Corresponding author:

Dr. Sayed Nour: Laboratory of Biosurgical Research (Alain Carpentier Foundation), Pompidou Hospital, 56 rue Leblanc, 75015 Paris, France. E-mail: nourmd@mac.com

Abstract

Objective Ischemic heart disease (IHD) is a leading cause of mortality with insufficient results of current therapies, most probably due to maintained endothelial dysfunction conditions. Alternatively, we propose a new treatment that promotes endothelial shear stress (ESS) enhancement using an intrapulmonary pulsatile catheter.

Materials and Methods Twelve piglets, divided in equal groups of 6: pulsatile (P) and non-pulsatile (NP), underwent permanent left anterior descending coronary artery ligation through sternotomy. After 1 h of ischemia and heparin injection (150 IU/kg): in P group, a pulsatile catheter was introduced into the pulmonary trunk and pulsated intermittently over 1 h, and irrespective of heart rate (110 bpm). In NP group, nitrates were given (7±2 mg/kg/min) for 1 h.

Results Animals survived ischemia for 120 min in P group vs. 93±14 min in NP group. Hemodynamics and cardiac output (CO) were significantly improved in P group compared with NP group: CO was 0.92±0.15 vs. 0.52±0.08 in NP group (L/min; $p<0.05$), respectively. Vascular resistances (dynes.s.cm^{-5} /kg) were significantly ($p<0.05$) lower in P group versus NP group: pulmonary resistance was 119±13 vs. 400±42 and systemic resistance was 319±43 vs. 1857±326, respectively. Myocardial apoptosis was significantly ($p<0.01$) lower in P group (0.66±0.07) vs. (4.18±0.27) in NP group. Myocardial endothelial NO synthase mRNA expression was significantly ($p<0.01$) greater in P group (0.90±0.09) vs. (0.25±0.04) in NP group.

Conclusions Intrapulmonary pulsatile catheter could improve hemodynamic and myocardial contractility in acute myocardial ischemia, regardless to coronary reperfusion. This represents a cost-effective method with low morbidity and mortality.

Keywords: Ischemic heart disease; Endothelial shear stress; Endogenous nitric oxide; Intrapulmonary pulsatile catheter; Heart failure.

Introduction

Angina pectoris is a historical presentation of ischemic heart disease (IHD), responsible for one death every 34 seconds, according to statistics from the United States [1,2].

Endothelial dysfunction is the main cause of IHD, including predisposing risk factors that usually induced due to disturbed endothelial shear stress (ESS), like atherosclerosis, diabetes, etc. [3-7].

The currently available strategies for IHD management can be summarized as based on 3-R principles: reperfusion of the ischemic zone, which is critically tied to time, and could be afforded pharmacologically (e.g. thrombolytic, nitrates), in addition to interventional and/or surgical procedures; rehabilitation of the cardiac pump to full function; and replacement of the damaged tissues partially (e.g. stem cell therapy), or completely as a final option with heart transplantation [8-12].

Despite medical advances and the escalating costs of IHD management, there is still a lack of impact with the current treatment. Insufficiency of current therapies is most probably, related to several influencing factors, such as: patients' diversity [13-18], therapeutic methods' drawbacks [19-23], and failure to restore the endothelial function [24]. For example, the atherosclerotic process continues and becomes worse even with radical procedures like endarterectomy or orthotopic heart transplant [25, 26].

As it is known, endothelium is the precursor of almost the entire cardiovascular system, heart included, it depends on adequate shear stress stimulations [27, 28].

In addition, several studies showed that patients with endothelial dysfunction had a considerably greater incidence of adverse cardiovascular events compared to patients with preserved endothelial function [29, 30].

In fact, IHD pharmacological options are functionally simulating what could be obtained naturally from the endothelium, but with side effects.

Alternatively, as a potential solution, we propose a new therapeutic approach, based on shear stress-mediated endothelial function stimulation.

This will be induced with a small pulsatile balloon catheter device, introduced into the pulmonary artery trunk as been previously detailed [31].

In this study we have compared traditional nitrates therapy versus an intrapulmonary catheter pulsation in a piglet model of acute myocardial ischemia.

We estimated hemodynamic improvements and salvage of the myocardial

ischemic zone in the treated pulsatile group.

Materials and Methods

Device and prototype

As been previously described [31], the balloon compartment of an intra-aortic balloon pump (IABP) catheter was peeled off and replaced by a small piece of commercial rubber balloon, with dimensions of 1 cm by 1 cm, to cope with pulmonary trunk geometries. The catheter prototype was connected to small animal ventilator, used as a generator, on one branch, and to a cardio-respiratory monitor on the other branch. The catheter was pulsated for checking air leakage in a saline bath, before being introduced into the pulmonary trunk through the right ventricular **(**RV**)** infundibulum.

Animal model

This study was approved by the Animal Research Facility at Sun Yat-Sen University and conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No.85- 23, Revised in 1996).

Twelve domestic piglets of both sexes were randomly designated to either pulsatile group (P, n=6; 8±0.63 Kg) or the non-pulsatile group (NP, n=6; 9.3±0.41 Kg).

Anesthesia

Animals were premedicated with an anesthetic mixture composed of dihydroetorphine hydrochloride, dimethylaniline thiazole, ethylenediaminetetraacetic acid, and haloperidol, (3 mL) and midazolam (0.5 mg/kg), given intramuscularly, then placed on a warmed operating table and surveyed with a rectal probe (38±1 ºC). Anesthesia was maintained by 3% sodium phenobarbital (1mg/kg), divided into doses and mechanical ventilation. Through a median cervicotomy and tracheotomy, a 3.5 – 5 # tracheal tube was inserted, followed by mechanical ventilation (PA-500 PuLang Technologies Inc®) with 40% oxygen, 10-15 ml/kg min tidal volume and 15/min respiration frequency. The right carotid artery was isolated; cannulation was performed with a 6 Fr arterial sheath. Then a Millar probe (4 Fr. MIKRO-TIP® catheter transducer, Millar Instruments) was introduced through the carotid line into

the aorta for continuous systemic pressure (AP) monitoring (BIOPAC® physiology monitoring system); this enabled other hemodynamic measurements mentioned below.

Surgical procedure

After median sternotomy, percardiotomy and dissection of great vessels, two purse string stitches (4/0 polypropylene), were positioned at the right atrium (RA) appendage and the infundibulum. A (5 Fr) double-lumen central venous line (Hydrocath™, B-D Tech.) was introduced through the RA purse string for drug administration and RA pressure monitoring. After heparin injection (150 IU/Kg), either a catheter prototype (in P group), or a 5 Fr. Swan-Ganz® (in NP group) was introduced through the RV infundibulum into the pulmonary trunk, guided by external palpation for pulmonary artery pressure (PAP) recording. Left atrium (LA) pressure was obtained by direct needle puncture at LA appendage. Cardiac output (CO) was measured with a TRANSONIC® transit-time flow meter temporarily positioned around the aortic root.

Both LA and CO measurements were obtained at pre-determined time points throughout the experiment as follows: T1=Baseline; T2=I h of Ischemia; and T3=I h of treatment.

Induction of ischemia

After surgical preparation, and data collection for T1, the left anterior descending coronary artery (LAD) was permanently ligated (4/0 polypropylene), distal to the 2nd diagonal bifurcation until the end of the experiment (2 h). Operative details are schematized in (Figure 1) and shown in the attached operative movie.

During the first 1 h of ischemia, ventricular fibrillation (VF) and cardiac arrest were frequent after 20-30 min of ischemia. Animals were assisted with classical cardio-pulmonary resuscitation (CPR) management, particularly DC shock (20-30 J), and without any further IHD supports. Animals that did not survive the first hour of ischemia were excluded.

Therapeutic phase

During the second hour of ischemia: in the P group, the catheter generator was switched on, at a fixed frequency (110 bpm) and irrespective of heart rate (74±11 bpm). Pulsations were delivered according to hemodynamic, intermittently and

interrupted by an interval pause of 10 min, with a global pulsation time of 15 -20 min over 1 h. Animals in the NP group were treated with a continuous intravenous infusion of nitroglycerin (10±2 µg/kg/min) for 1 h.

Hemodynamics

Data were collected from both groups at T1, T2 and T3 including: AP, PAP, LA, and RA pressures, heart rate and CO. The vascular resistance index was calculated with the flowing formula:

Pulmonary vascular resistance index (PVRI) = 80* (MPAP – PCWP) / CO*Wt

Systemic vascular resistance index (SVRI) = 80* (MAP – CVP) / CO*Wt

Where: MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure, substituted for LA pressure; MAP = mean arterial pressure; CVP = central venous pressure, substituted for RA pressure; CO = cardiac output; and Wt = body weight.

Histopathological Investigations

The ischemic zone was measured and evaluated macroscopically during T2 and T3. Upon completion of 2 h in P group, or just before severe hemodynamic deterioration in NP group, animals were euthanized with a 10 ml injection of saturated potassium chloride (KCl). Tissue samples of myocardial, pulmonary and aortic tissues were collected for histopathological and electromicroscopic analyses as follows:

- *Myocardial eNOS mRNA Expression*

Total RNA was isolated from cells with Trizol reagent (Invitrogen, USA) following the manufacturer's protocol. The RNA concentration was determined spectrophotometrically at 260 nm. Of the total RNA, 3 µg was used in a reverse transcription kit according to manufacturer's instructions (Reverse Transcriptase M-MLV®, TaKaRa). Primers were specifically designed for the porcine model with the following sequences:

eNOS, sense 5'-GTGGAAATCAACCTGGCTGT-3';

antisense 5'-AAACGTCTTCTTTCTGGCGA-3';

β-actin, sense 5'-CACCCGTCTTCAGGGCTTCTTGGTTT-3';

antisense 5'-CATTTCACCATCTGGTTGGCTGGCTC-3'.

The eNOS mRNA was amplified by PCR with the TGRADIENT® Thermo Cycler system (Whatman Biometa Inc., Germany).

The amplification profile was 94°C for 3 min (denaturation), and then 40 cycles of: 94°C for 30 s (denaturation), 55°C for 30 s (primer annealing), and 63°C for 30 s (elongation): followed by 72°C for 5 min (extension). Negative controls were conducted in parallel with a similar profile, except that elongation at 72°C was for 30 s, and réactions were run for 25 cycles. For quality control, PCR products were analyzed by electrophoresis on a 2% TAE gel. The data were normalized to β-actin levels to account for differences in reverse transcription efficiencies and amounts of template in the reaction mixtures.

- Myocardial Apoptosis

Myocardial tissue from the ischemic region was placed in 10% buffered formalin for 24 h, then mounted in paraffin and sectioned in 4 μm slices. The apoptotic cells were identified with a terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) apoptosis detection kit according to the manufacturer's protocol (Boster Inc, China). Five photographs (magnification 20×) were taken of each tissue section. All TUNEL-negative (blue) and TUNEL-positive (brown) nuclei were visualized under a light microscope; the total number of nuclei counted in 5 random high-power fields from each sample. The apoptotic index (AI) was calculated as 100%*(TUNEL-positive nuclei / all nuclei).

- Endothelial nitric oxide synthase (eNOS) Staining

Immunohistochemical staining of eNOS protein was performed on paraffin-embedded 4 μm sections of pulmonary artery ring samples. Rabbit anti-eNOS polyclonal antibody (Bioss, Biotech., China) (1:1000) was incubated with sections overnight at 4°C. The sections were then incubated with a secondary label biotinylated horse anti-rabbit antibody (DAKO Germany) for 30 min at room temperature. Horseradish peroxidase-conjugated avidin (30min, at room temperature) and diaminobenzidine (6min, room temperature) were used for visualization (DAKO, Germany). Sections were counterstained with hematoxylin (blue color) for 1 minute. The specific staining of individual sections was evaluated by light microscopy.

Transmission Electron Microscopy

Fresh myocardial tissue samples were collected, and a 0.5-1 mm^3 section was rapidly excised, fixed in 3% glutaraldehyde, and stored at 4 ºC. The next day, fixed samples were sent to the Electron Microscopy Laboratory at the North Campus of the Sun Yat-Sen University for sample preparations. Transmission electron microscopic (TEM) images were obtained from the TEM Laboratory (CM-10, Philip, Germany).

Statistics

Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test for eNOS and TUNEL studies and a 2-way ANOVA for hemodynamic data. P with a value less than 0.05 were considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

RESULTS

None of the animals in P group showed complications related to the insertion of the intrapulmonary pulsatile catheter device (Figure 2).

All animals in P group survived 120 min of ischemia, with macroscopic clearance of the ischemic zone (Figure 3), versus 93±14 min of survival in the NP group.

The hemodynamic profiles of the two groups were assessed at three different time points (Table 1). CO dropped significantly after surgical ligation (T2) compared to baseline (T1); this reflected massive loss of myocardial contractility due to acute ischemia.

Mean arterial pressure (MAP) and mean pulmonary arterial pressure (MPAP) remained nearly constant at T2 compared to T1. In NP group, they remained nearly constant at T3. However, in P group, both MAP and MPAP decreased significantly at T3, with a concomitant increase in CO, compared with NP group; this led to significant drops in SVRI and PVRI (Figure 4). Between-groups, comparisons of all the measured and calculated variables were similar at T1 and T2 ($p > 0.05$), indicating a homogeneity and success of the animal model. At T3, the MAP, MPAP, LAP, CO, SVRI and PVRI were significantly different between groups ($p < 0.05$).

The apoptotic index (AI) in P group was significantly ($p<0.01$), lower than that of NP group; AI was 0.66±0.07 versus 4.18±0.27, respectively (Figure 5).

The eNOS mRNA expression was significantly ($p<0.01$) increased in P group compared to NP group. The ratio of eNOS versus beta actin OD values in P group was 0.90±0.09, compared to 0.25±0.04 in NP group (Figure 6).

One random case from each group was selected for immunohistochemistry of endothelial nitric oxide synthase (eNOS). In P group, but not in NP group, the pulmonary artery ring revealed positive staining (Brown) for eNOS in the inner linen of the cross sectioned artery. This indicated enhanced expression of eNOS in the pulsated pulmonary endothelium (Figure 7).

Transmission Electron Microscopy showed that acute myocardial ischemia resulted in an immediate and serious injury to the myocardium. At the microstructural level, the NP group tissues exhibited severe fraying and/or disintegration of myofibrils and intercellular organelles, considerable Z band thickening and streaming, significant mitochondrial swelling with deranged cristae. In contrast these injuries were less severe in P group (Figure 8).

DISCUSSION

This preliminary study proved the feasibility and effectiveness of the intrapulmonary pulsatile catheter as a new therapeutic approach in acute myocardial ischemia.

Besides, significant improvement of hemodynamic in the pulsatile group (P) compared to nitrates group (NP), the study revealed some positives points that deserve further analysis.

It remains controversial whether patients can benefit from intrapulmonary artery balloon pulsation, using an IABP [32].

In our study the intrapulmonary pulsatile catheter was applied successfully as a shear stress-mediated endothelial function enhancement device. For this application we have designed a small balloon catheter prototype to cope with diameters and types of wall vessels, particularly in a high compliant pulmonary artery trunk [33]. The purpose of the pulsatile catheter prototype was to induce rapid shear rates at stagnant blood boundaries layers of the PA, according to the Bernoulli's principles of shear stress, and to avoid volume distension (pulse pressure) at the right heart circuit, according to Newton's law [34].

As known, the main impact of endothelial shear stress (ESS) is up-regulation of endothelial nitric oxide synthase (eNOS) expression, which leads to an increase in NO release [35, 36]. Cardiovascular effects of NO include direct vasorelaxation, inhibition of platelet adhesion and aggregation, and the maintenance of endothelial function, vascular growth, and myocardial contractility [37, 38].

Endogenous NO could be physiologically induced by physical exercise, as a result of eNOS activation [39].

Meanwhile, exogenous NO donors can also induce eNOS, directly (e.g. inhaled NO, sodium nitroprusside); or indirectly through several metabolic processes like organic nitrate, ACE Inhibitors, phosphodiesterase-5 inhibitors [40-42].

Typically, patients with IHD exhibit other endothelial pathology, which can significantly reduce the bioavailability of NO in response to drugs [43, 44]. In addition nitrates' tolerance may develop rapidly during sustained therapy [45]. This subject is intensely debated but remains poorly understood

Recent studies showed that nitrates played an important role in tissue NO storage, which reduced myocardial ischemia–reperfusion injury [46]. However, when substrates and co-factors are depleted, NOS may induce oxygen free radicals

instead of NO.

The results of our study showed that an endogenous NO therapy, which could be induced with an intrapulmonary catheter, was effective and superior to exogenous NO donors (nitrates), in acute IHD syndrome. Superior survival from ischemia in P group could be explained by the increased production of endogenous NO as been confirmed with the increased expression of myocardial eNOS mRNA; fewer apoptotic cells, and increased expression of eNOS protein in PA segments.

This mechanism of myocardial recovery may be related to vascular endothelium that controls coronary artery function and indirectly cardiac function by controlling the coronary myocardial blood supply [47]. Alternatively, it could be also related to the cardiac endothelium in myocardial capillaries and in the endocardium, which is adjacent to cardiomyocytes to allow direct cellular communication and signaling between cell types [48]. However, the exact mechanisms of action remain to be explored, as this hypothesis of presumed pulmonary eNOS traveling into the systemic circulation could be refuted by the short biological lifetime of NO [49, 50].

Contrarily to current ischemic models using adult animals [51], we have created an acute MI by coronary artery obstruction in a pediatric model with immature myocardium [52] well known for poor collaterals [53], that induced a cardiogenic shock.

On the other hand, the subendocardial resistance vessels are more sensitive to mediators of vasodilatation and endothelium dependent dilators [54].

All these may promote the important role of the subendocardial capillaries and myocardial microcirculation in hemodynamic improvement of the P group, rather than coronary collaterals networks flow.

Interestingly, the study results showed that immediate myocardial reperfusion might be unnecessary. As it is known, the excessive NO, which is usually produced following ischemia/reperfusion, is involved in inflammatory cardiomyopathies and myocardial dysfunction [55, 56].

These was proved with animals survival from a cardiogenic shock state until the end of experiment in the P group (120 min), and contrarily to NP group (93 ± 14 min), were manifested by better contractility and CO, despite the maintained coronary obstruction and frequent cardiac arrest. Progressive clearance of the infarcted zone in P group (Figure 3) was associated with low myocardial apoptosis, and relatively well-preserved cardiomyocytes organelles. Remarkably, one case that

showed disturbed hemodynamics at T1 showed improvement after pulsation at T3 even with LAD ligation (refer to the movie: http://www.nourmd.com)

Compared to current management of IHD using percutaneous transluminal coronary angioplasty (PTCA), the proposed catheter device could be introduced into the pulmonary artery trunk like a central venous line in hospital setting; afterwards it could be connected to a small portable-implantable pulsatile generator. This means patients would benefit from real-time hemodynamic measurements and simultaneous therapeutic pulmonary pulsation. Such venous approach promises less morbidity, compared to current interventional procedures (e.g. PCI and/or IABP), which require specific operative environments and arterial approach with high risk of complications [57, 58].

We should emphasize that hemodynamic stabilization could be achieved after a few minutes of device pulsations without further medical supports, reducing the pulmonary artery afterload without jeopardizing preload like in case of RV ischemia. The small balloon dimensions allow its applications in pediatrics and other cases of non-atherosclerotic IHD (e.g. congenital, coronary spasm, or vasculitis, etc.).

The device does not require cardiac synchronization like in case of current pulsatile CADs (IABP, EECP), which are unsuitable in case of arrhythmia. The recorded pressure curves showed that the delivered catheter pulsation was faster than the heart rate; nevertheless, it did not disturb right ventricular hemodynamic or obstruct the RV outflow tract. We believe that unsynchronized catheter pulsation simplifies and broadens its application as an efficient cost-effective method for IHD management.

On short-term, the device provides immediate improvement of hemodynamic and myocardial microcirculation. Over the long-term, shear stress-induced endothelial regulation, alone or in combination with angiogenic growth factors or progenitor stem cells [59] may promote cardio-circulatory rehabilitation and accelerate cardiogenesis. On another term, a longer period of an intermittent intrapulmonary catheter pulsation may restore myocardial tissues and dysfunctional endothelial coronary lesions in preconditioned, hibernating, stunned myocardial or chronic IHD [60, 61].

In future investigations, the device could be inserted in an atherosclerotic model, either associated or not with an absorbable stent, for flow dynamics-endothelial function restoration, like in atherosclerotic pathogenesis. This concept is

supported by the results obtained with EECP in atherosclerotic animal models [62].

Finally, as far as the concept has been proven therapeutic efficiencies, there were some limitations, that may be related to experiment's novelty and undiscovered endothelial mediators. This includes the rapid drop of systemic vascular resistances as a result of the intrapulmonary endothelial stimulations. A similar phenomenon has been observed with Nicorandil, an exogenous NO donor used for angina pectoris relief [63]. The drop of both systemic and pulmonary vascular resistances in group P proves the hypersensitivity of the pulmonary endothelium to the unsynchronized stimulations, compared to reported results from systemic arteries pulsatile devices like IABP and EECP [64].

Currently, we have overruled this phenomenon, with a smaller balloon catheter (Figure 9), and shorter pulsatile time, interrupted by interval pause according to hemodynamics, particularly the systemic arterial pressure.

Improvements

The study concept deserves further evaluations with more enlarged investigations. In our ongoing studies, we use a PCI technique to create and treat acute MI in pig model using a biodegradable glue LAD blockage, and a trans-jugular intrapulmonary pulsatile catheter approach.

Conclusions

An intrapulmonary pulsatile catheter could be used as a new therapeutic method for acute IHD management. Comparing the advantages of the proposed therapy with the drawback oftraditional IHD management, this would represent a nearly physiologic and cost-effective method.

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Table1 :

	T1		T2		T3	
GROUPS	**P**	**NP**	**P**	**NP**	**P**	**NP**
Wt* (kg)	8.00±0.63 ‡	9.30±0.41	Nd	nd	nd	Nd
HR* (bpm)	73.20±8.79 ‡	77.60±7.35	74.20±11.09 ‡	98.00±9.97	79.00±8.30 ‡	78.60±6.93
MAP* (mmHg)	68.00±7.64 ‡	77.47±5.75	66.80±15.84 ‡	82.02±8.54	28.60±6.64	82.87±15.02 §
MPAP* (mmHg)	19.80±2.65 ‡	22.85±1.36	21.00±3.08 ‡	29.95±2.82	13.20±1.46	24.79±2.39 §
LAP* (mmHg)	3.54±0.66 ‡	3.10±0.40	2.78±0.39 ‡	8.08±0.52	1.02±0.54	4.18±0.86 §
RAP* (mmHg)	3.40±0.89 ‡	1.94±0.29	3.86±0.71 ‡	4.33±1.62	4.10±2.23 ‡	3.46±0.94
CO* (L/min)	0.84±0.09 ‡	0.84±0.05	0.50±0.07 ‡	0.57±0.07	0.92±0.15	0.52±0.08 §
SVRI† (d.s.cm^{-5}/kg)	772.14±23.32 ‡	777.25±40.75	1265.10±233.95 ‡	1184.69±128.89	298.71±81.43	1308.26±181.31 §
PVRI† (d.s.cm^{-5}/kg)	189.83±18.24 ‡	206.36±18.01	411.19±100.10 ‡	341.32±51.79	145.19±15.25	379.38±74.89 §

Table1 : Summary of Hemodynamic results:

P: pulsatile treatment group; NP: non-pulsatile, nitrate treatment; Wt: weight; nd= not measured ; HR: heart rate; MAP: mean arterial pressure; MPAP: mean pulmonary arterial pressure; LAP: left atrial pressure; RAP: right atrial pressure; CO: cardiac output; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index.

*measured variables; †calculated variables; ‡P > 0.05 between the P and NP groups; §P < 0.05 between the P and NP groups. T1: baseline; T2: 1 h after ligation; T3: 1 h after treatment.

Legends of Figures:

Figure 1: Presumed mechanism and passage of induced pulmonary eNOS

1 = Pulmonary artery (PA); 2 = pulsatile catheter fitting PA trunk; 3 = right ventricle (RV) inlet-outlet compartments; 4= infundibular site of pulmonary catheter insertion; 5 = arrows showing presumed passage of pulmonary eNOS (backward through coronary ostia and/or forward through systemic circulation); 6 = left ventricle (LV) inlet-outlet compartments; 7 = permanent ligation of the left anterior descending coronary artery distal to the second diagonal branch; 8 = interventricular septum; 9 = cardiorespiratory monitor; 10 = pneumatic driving force.

I = pulmonary eNOS primarily induced at PA zone with catheter pulsation; **II** = pulmonary eNOS natural passage through the left heart circuit; **III** = presumed pulmonary eNOS involvement in myocardial recovery most probably through microcirculation and/or the RV interseptal coronary network.

Figure 2: Right ventricular pressure (RVP) monitoring during pulmonary pulsation

Upper panel, RVP at experiment time 9990s; lower panel, RVP at experiment time 10700s. Right ventricular pressure was not affected by the pulmonary catheter pulsation.

Figure 3: Macroscopic reduction of the ischemic zone

A = left panel figure showing dark infarcted myocardial after 50 min of ischemia; B = right panel figure showing significant reduction of ischemic myocardial zone after 10 min of pulsation; 1 = left anterior descending coronary artery snugger; 2 = infundibular site of the intrapulmonary pulsatile catheter insertion.

Figure 4: Main hemodynamic results at three different time points

P = pulsatile group (red color); NP = non-pulsatile group (blue color); T1 = baseline; T2 = 1 h of ischemia; T3 = end of experiment (2 h); PAP = mean pulmonary artery pressure (upper left panel); AP = mean aortic pressure (middle left panel); CO = cardiac output (lower left panel); PVRI = pulmonary vascular resistance index (right upper panel); and SVRI = systemic vascular resistance index (lower right panel). Both PVRI and SVRI increased significantly after acute myocardial infarction. However, group P demonstrated a significant drop in both readings after pulsatile

treatment, whereas in group NP both levels almost doubled at the end of study (both $P<0.01$).

Figure 5: Myocardial apoptosis by TUNEL technique

Upper panel, apoptotic index (AI) in both groups. AI in group P was significantly lower than that in group NP ($P<0.01$); lower panel, representative figures from both groups showing apoptotic cells manifestations (red arrows): lower left, group P, lower right, group NP.

Figure 6: Myocardial eNOS mRNA expression

RT-PCR results shown with statistics, in which myocardial eNOS expression was significantly higher in group P compared to group NP ($P<0.01$).

Figure 7: Pulmonary eNOS immunohistochemistry of one random case from each group

Upper two panels, magnification 40x; lower two panels, magnification 100x. Left two panels, group P; right two panels, group NP.

Figure 8: Myocardial microstructure visualized with transmission electron microscopy

Left panels: samples from the non-pulsatile, nitrate treatment group (NP); right panel: sample from the pulsatile treatment group (P). Notice the relatively well-preserved myocardial microstructure in group P. Bar scale on each graph equals one micrometer.

Figure 9: Current intrapulmonary pulsatile catheter prototype

Left (A) and Right (B) panels, showing the balloon catheter with its guide-wire, inflated and deflated respectively.

Electronic Supplementary Material

Click here to download Electronic Supplementary Material: Acute MI (piglets).m4v

Figure
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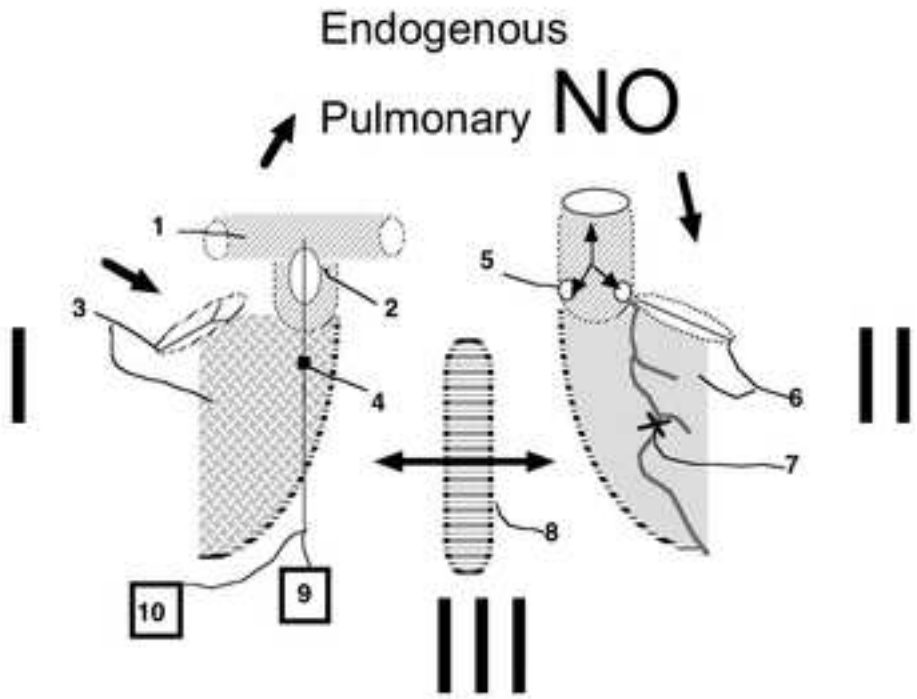

Figure 1

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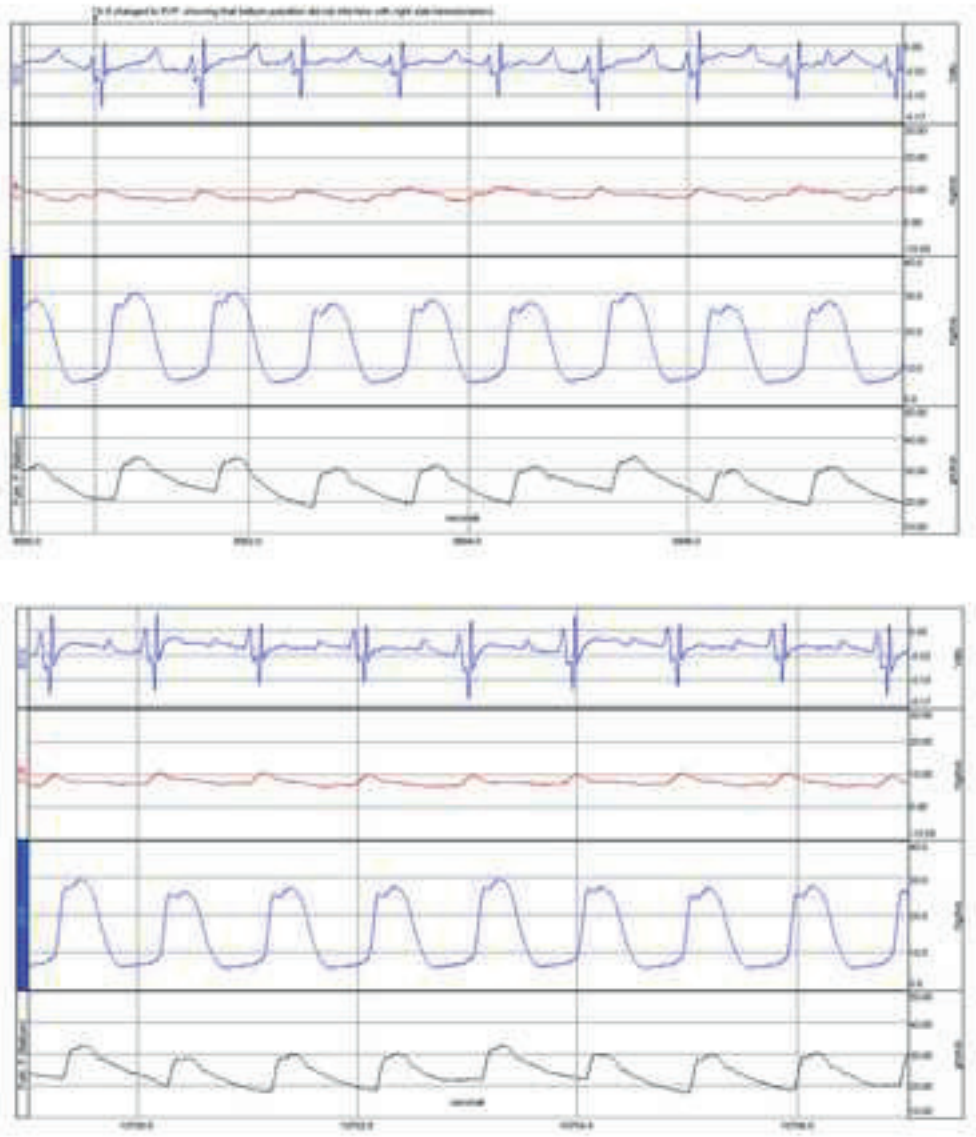

Figure 2: Right ventricular pressure (RVP) monitoring during pulmonary pulsation.

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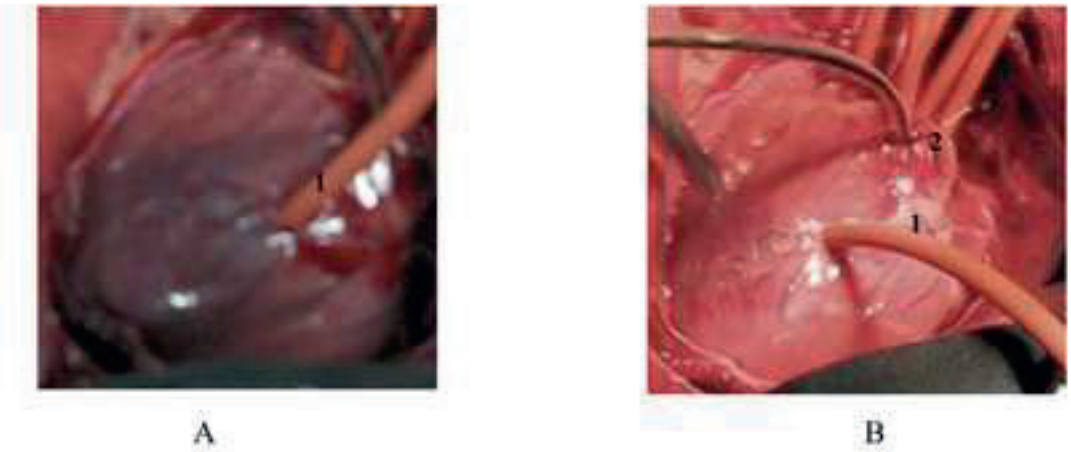

A B

Figure 3

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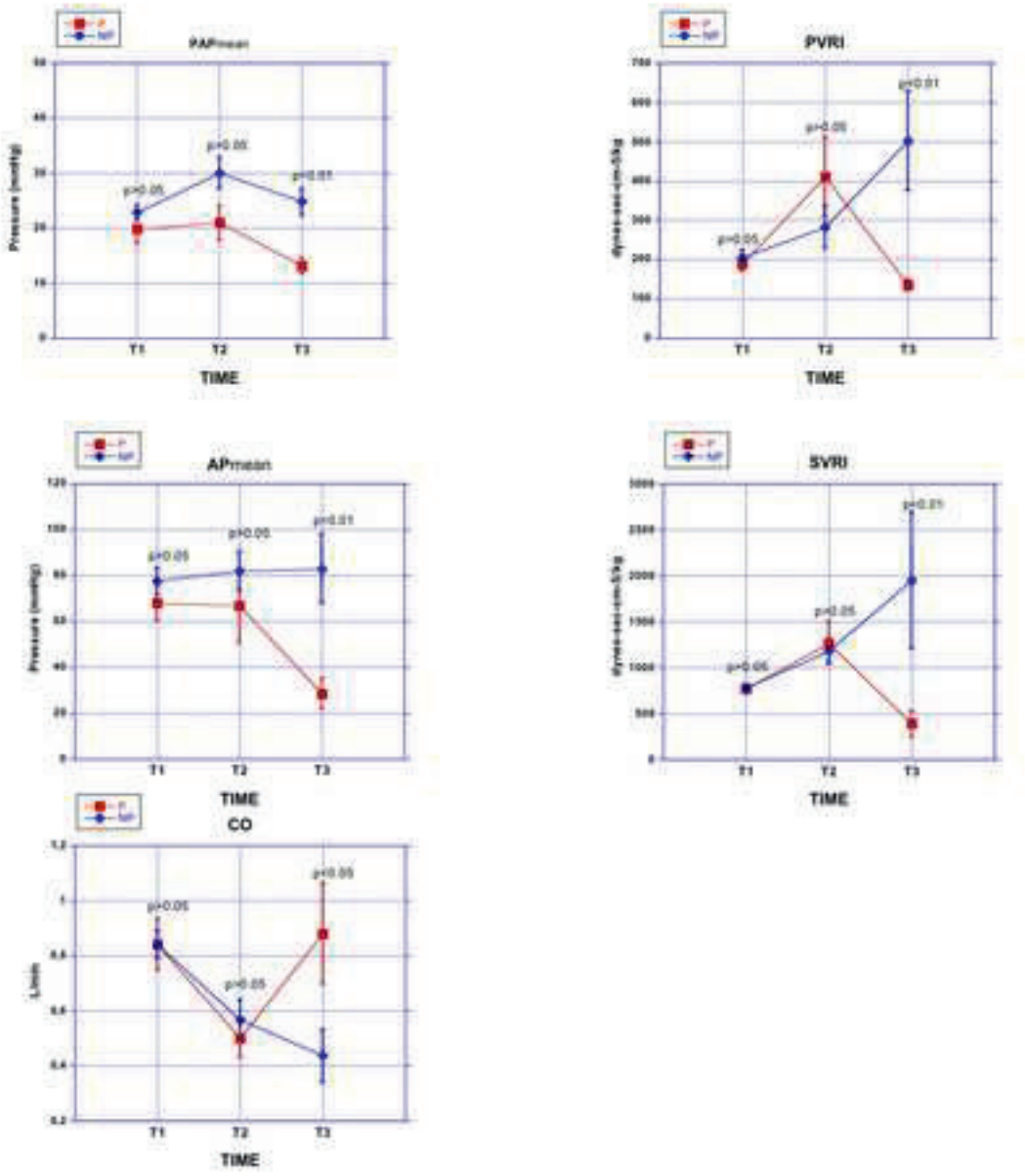

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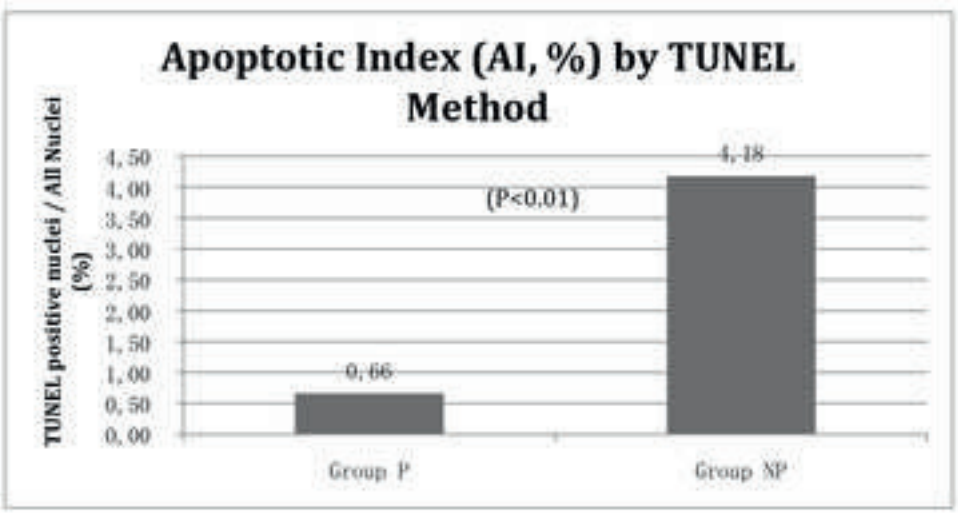

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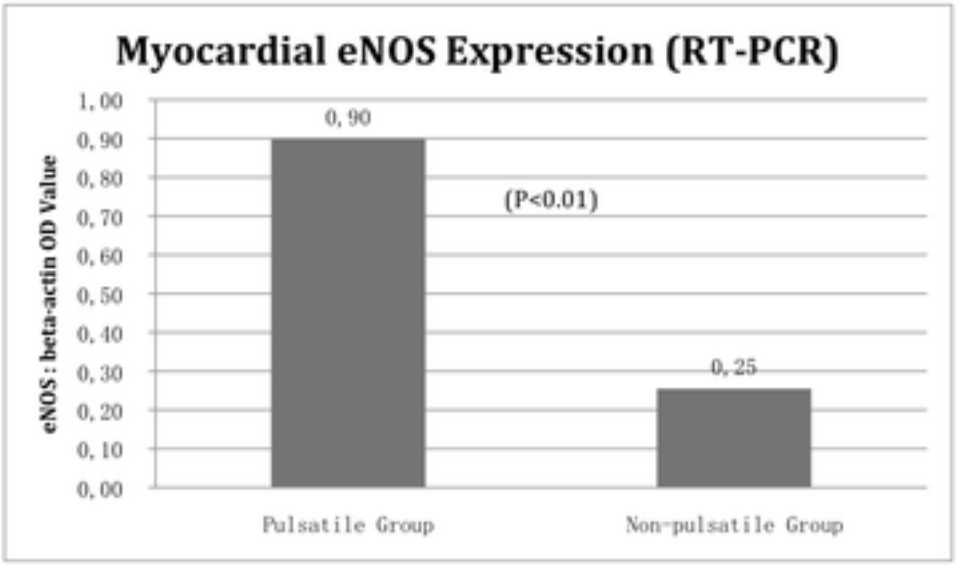

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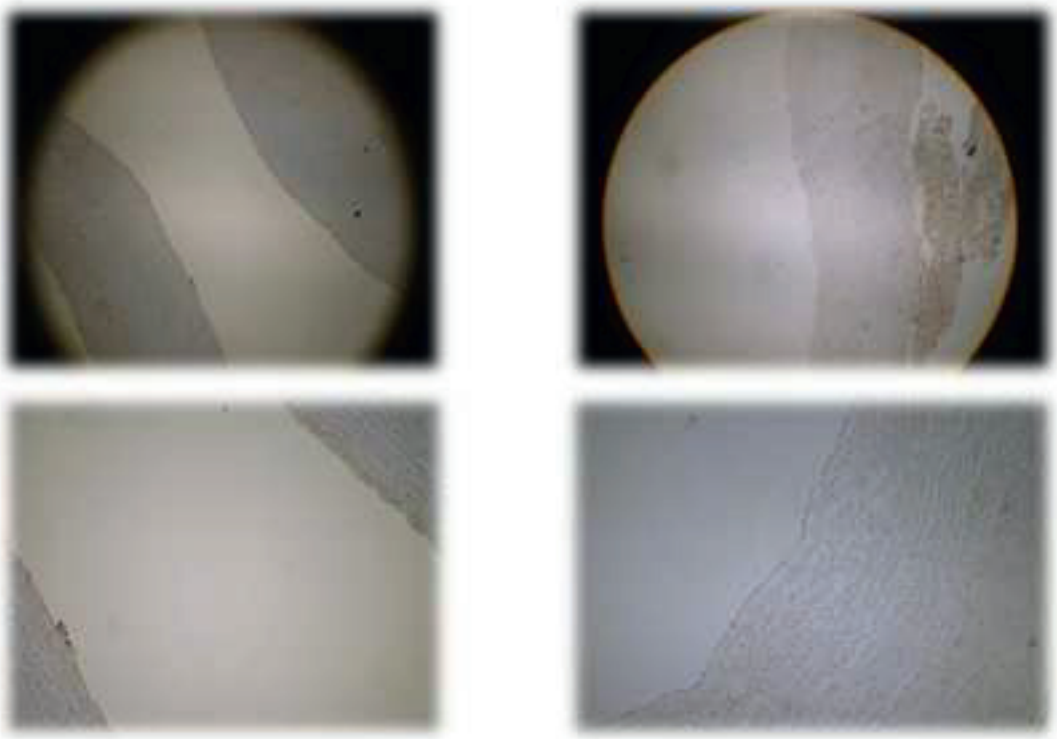

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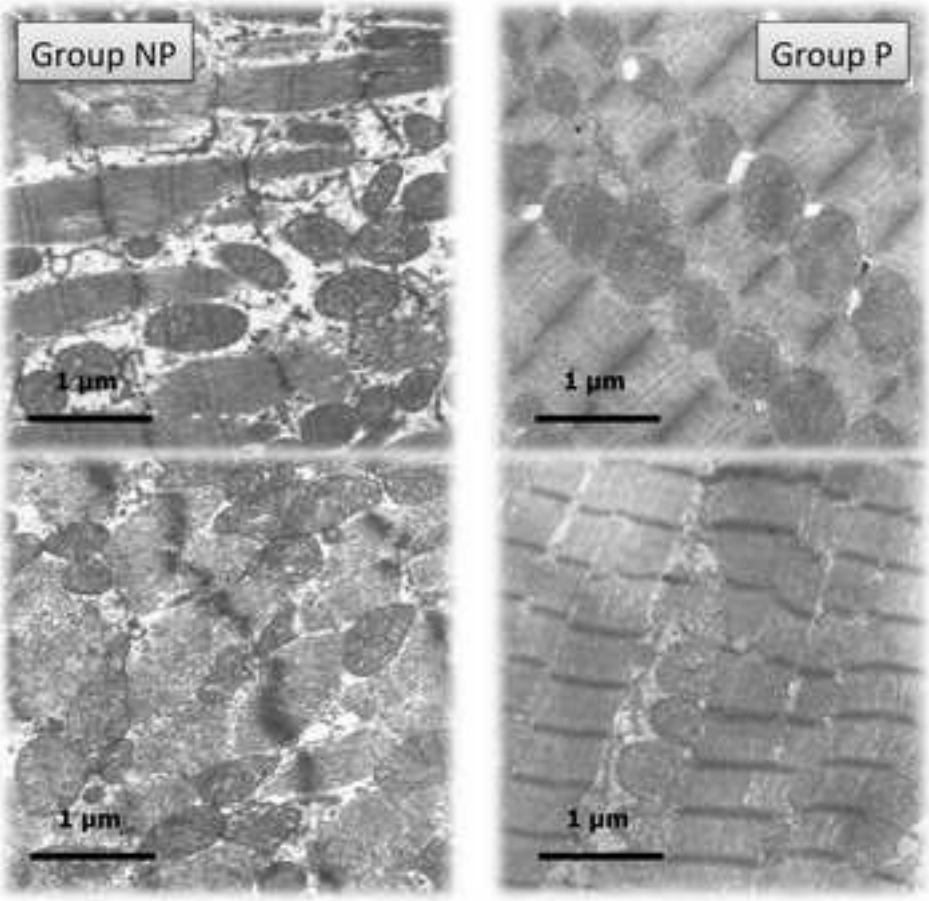

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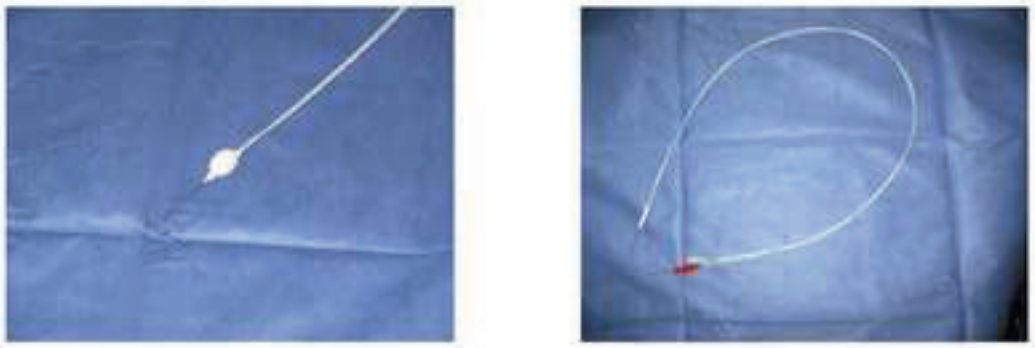

A B

Figure 9: Intrapulmonary pulsatile Catheter (new prototype)

Intrapulmonary Shear Stress Enhancement: A New Therapeutic Approach in Pulmonary Arterial Hypertension

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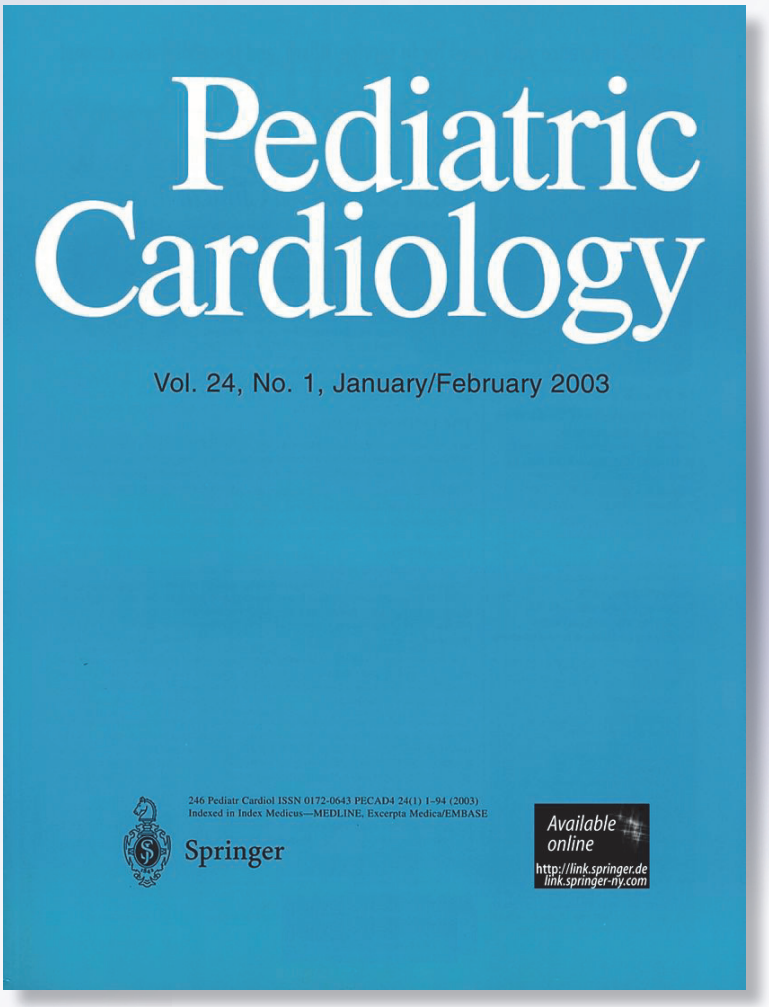

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ORIGINAL ARTICLE

Intrapulmonary Shear Stress Enhancement: A New Therapeutic Approach in Pulmonary Arterial Hypertension

Sayed Nour · Gang Dai · Daniel Carbognani · Minze Feng · Daya Yang · Nermine Lila · Juan Carlos Chachques · Guifu Wu

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Abstract
Objective Pulmonary arterial hypertension (PAH) is a dysfunctional endothelium disease with increased pulmonary vascular resistance (PVR) and poor prognosis. Current therapies are still insufficient. Here we propose a new pulsatile device as a more effective tool for PAH management compared with traditional treatments.
Materials and Methods Twelve piglets (10.3 ± 3.8 kg) were given either intrapulmonary pulsatile [P ($n = 6$)] or nonpulsatile [NP ($n = 6$)] tadalafil treatment. After median sternotomy and heparin injection (250 IU/kg), both groups underwent aorto-pulmonary surgical shunt for 1 h. During a second 1 h period in group P, a catheter prototype, driven by a small ventilator, was introduced into the pulmonary trunk and pulsated intermittently at 110 bpm irrespective of heart rate (90.6 ± 10.74 bpm). In group NP, tadalafil was given orally (1 mg/kg).
Results Hemodynamics and cardiac output (CO) were significantly ($p < 0.05$) improved in group P compared with group NP: CO was 0.56 ± 0.0.26 versus 0.54 ± 0.11 (L/min), respectively. Mean pulmonary artery pressure (PAP) was decreased in group P compared with group NP: PAP was 9.6 ± 2.97 versus 32.2 ± 5.07, respectively. Vascular resistances (dynes.s.cm^{-5}/kg) were significantly lower in group P versus group NP: pulmonary resistance was 85 ± 42.12 versus 478 ± 192.91 and systemic resistance was 298.8 ± 172.85 versus 1301 ± 615.79, respectively. Using Western blot analysis, endogenous NO synthase expression in PA segments was nonsignificantly ($p > 0.05$) greater in group P (0.81 ± 0.78) versus (0.62 ± 0.35) group NP.
Conclusion Induced with an appropriate device, intrapulmonary shear stress–mediated endothelial function enhancement provides a more effective nearly physiological therapy for PAH.

Keywords Pulmonary arterial hypertension · Intrapulmonary pulsatile catheter · Shear stress · Endothelial function

Introduction

Pulmonary arterial hypertension (PAH) is a cardiopulmonary disease characterized by increased mean pulmonary arterial pressure (PAP) ≥ 25 mmHg and pulmonary vascular resistance (PVR) ≥3 Woods units at rest [1]. Etiologically, PAH is classified according to the underlying pathology into five groups and several subgroups, most commonly represented in patients with left-sided heart pathologies and congenital anomalies [2]. Currently, PAH is recognized as an endothelial dysfunction disease with a dismal prognosis comparable with that of advanced cancer [3, 4].

Decreased PVRs and enhancement of gas exchanges represent the main target of current PAH therapies. This could be achieved pharmacologically with the nitrous oxide (NO)–cGMP pathway and the prostacyclin–cAMP and endothelin receptors antagonists [5]. Inhalational NO

S. Nour (✉) · D. Carbognani · N. Lila · J. C. Chachques
Laboratory of Biosurgical Research (Alain Carpentier Foundation), Pompidou Hospital, University Paris Descartes, 75015 Paris, France
e-mail: nourmd@mac.com

S. Nour · G. Dai · M. Feng · D. Yang · G. Wu
Key Laboratory on Assisted Circulation, Division of Cardiology, Ministry of Health of China, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan Rd II, 510080 Guangzhou, China

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(iNO) is widely applied in postoperative PAH management [6]. In addition, oral administration of phosphodiesterase-5 (PDE5) inhibitors proved effective in PAH patients and in animal models [7, 8], and it has been shown that a combination of inhaled, long-acting prostacyclin analog and oral PDE5 might be helpful in some resistant cases [9]. Nonpharmacological supports, along with the employment of mechanical-assist devices and/or surgical procedures, may be needed in critical hemodynamic cases [10].

Unfortunately, management of PAH may improve symptoms and hemodynamic parameters, but it does not decrease mortality [11]. For example, iNO, which relaxes arterial smooth muscle in the absence of parenchymal lung disease, could increase endothelin-1 levels and decrease endogenous nitric oxide synthase (eNOS) activity [12]. Abrupt discontinuation of iNO can result in rebound PAH with further deterioration of hemodynamic [13, 14]. Other relatively recent drugs, such as inhaled iloprost, may cause acute bronchoconstriction, and one must be cautious in pregnancy with some drugs, such as bosentan [15]. These controversies surrounding inhalational PAH therapies may be explained by the different behavior of the extra-alveolar and alveolar endothelial cells due to their different embryological origins [16]. The drawbacks of PAH management have increased the demand for new strategies, particularly the enhancement of pulmonary endothelial NO release [17, 18]. In fact, these pharmacological therapeutic PAH options simulate what can be obtained naturally from the endothelium, but they have side effects.

Alternatively, and as a potential solution, we propose a shear stress–mediated endothelial function therapy for PAH patients. Normally, shear stress–mediated endothelial function could be induced physiologically during physical exercise, which improves cardiac output (CO), organ performance, and general metabolic processes [19]. Meanwhile, clinical applications of endothelial shear stress (ESS) with cardiac-assist devices (CAD) are controlled by several diversities between the cardiovascular system and lumped models [20]. These include inconstant blood viscosity, flexible vessels with variables diameters, and different circulatory driving forces [21].

Thus, successful delivery of pulmonary ESS must overrule three conditions: (1) compliant PA zone; (2) pulmonary volume overloads; and (3) right-ventricular outflow tract obstruction (RVOTO). This could be induced with a small intrapulmonary pulsatile catheter to increase tangential friction forces at the inner PA boundaries.

This study is based on the concept of an intravascular shear rate–enhancement device, i.e., a device composed of a small-size balloon catheter driven by a portable or implantable generator (Fig. 1). An intrapulmonary pulsatile device was tested in pediatric piglets with acute PAH and the results compared with another group treated with a phosphodiesterase-5 inhibitor (tadalafil). The goal of this study was to evaluate the efficiency of the intrapulmonary pulsatile catheter versus pharmacological therapy (tadalafil).

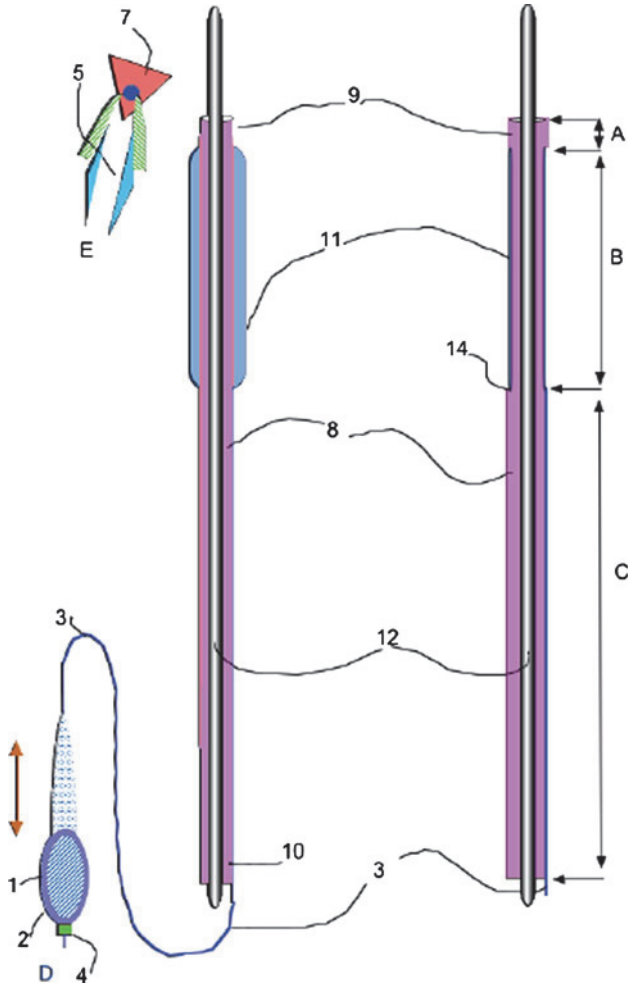

Fig. 1 Intravascular shear rate–enhancement device. (*Right*) A catheter device shaft that has an unfolded small-size balloon membrane at its proximal end. (*Left*) Full descriptive schemata of the pulsatile catheter with proximal balloon inflated, distal prefilled reservoir, guidewire, and small implantable driving force. According to patents descriptions (World Intellectual Property Organization : WO 2009/136034 and WO 2009/136035): A device for creating a pulsating inflation of an inflatable component (*11*) of a catheter (*8*) comprising a bag (*1*) that can be filled with fluid (*2*); a bag compression means (*5*) capable of compressing said bag (*1*) in a pulsed manner; and a connection means (*3*) connecting said bag (*1*) to said inflatable component (*11*) of the catheter (*8*) and allowing the fluid (*2*) to move between said inflatable component (*11*) and said bag (*1*). *A* proximal part, *B* balloon groove, *C* proximal part, *D* prefilled bag, *E* generator

Materials and Methods

Device Prototype

A standard intra-aortic balloon pump (IABP) catheter (8F, 30 cc) was modified. Briefly, its original balloon membrane

was peeled off and replaced with a small piece (1.5 cm length) of a commercial rubber balloon that was stretched and tied manually at each end of the catheter. A cardiorespiratory monitor (Biopac systems, Inc) was connected at one of the distal branches of the catheter. A small animal ventilator (HX-300; TaiMeng Technologies) was connected at the other distal branch. The ventilator was fixed at a frequency of 110 bpm and an adjustable inflation/deflation volume according to the requested balloon dimension. An inflated balloon dimension of 1×1 cm was enough to handle the pulmonary artery (PA) trunk geometries without obstructing the RVOT. The whole set was tested for leakage, while pulsating in a heparinized saline bath, before being inserted into the pulmonary trunk.

Shunt System

We used a "U"-shaped shunt (Fig. 2a) composed of two polyvinyl chloride (PVC) tubes with the following dimensions—diameter =1/16 inch and length =4 cm for aortic and 3.5 cm for pulmonary limbs—to avoid vessel torsions of the aortic limb of the shunt, which was longer than the pulmonary limb. The two limbs of the shunt were connected to each other with a flexible silicon tube (1/16 inch, 2 cm length). A three-way stopcock was positioned at each angle of the shunt ($n = 2$) for de-airing, pressure monitoring, and frequent heparin injection.

Animal Model

This study was approved by the Animal Research Facility at Sun Yat-Sen University and conformed to the Guide for the Care and Use of Laboratory Animals [National Institutes of Health Publication No. 85–23 (revised in 1996)]. Twelve domestic piglets of both sexes were randomly designated to either the pulsatile (P) group ($n = 6$, weight 10.5 ± 0.58 kg) or the nonpulsatile (NP) group ($n = 6$, weight 10.6 ± 1.85 kg).

Anesthesia

Animals were premedicated with an anesthetic mixture of dihydroetorphine hydrochloride, dimethylaniline thiazole, ethylene diamine tetraacetic acid, haloperidol (3 mL), and midazolam (0.5 mg/kg), which was given intramuscularly. Animals were placed on a warmed operating table and surveyed with a rectal probe (38 °C ± 1 °C). Anesthesia (3 % sodium phenobarbital 1 mg/kg) was divided into doses and injected through a peripheral venous line. After a median cervicotomy and tracheotomy, a pediatric endotracheal tube (size: 3.5–5 Fr), was inserted, followed by mechanical ventilation (PA-500; PuLang Technologies) with 40 % oxygen, 10–15 ml/kg min tidal volume, and 15/min respiration frequency. The right carotid artery was isolated, and a 6F catheter was introduced. Then a Millar probe (4F MIKRO-TIP catheter transducer; Millar Instruments) was introduced through the carotid line into the aorta for continuous systemic pressure (AP) monitoring (Biopac physiology monitoring system); this enabled other hemodynamic measurements mentioned later in the text. In the first cases from group P, we introduced another Millar catheter (3F

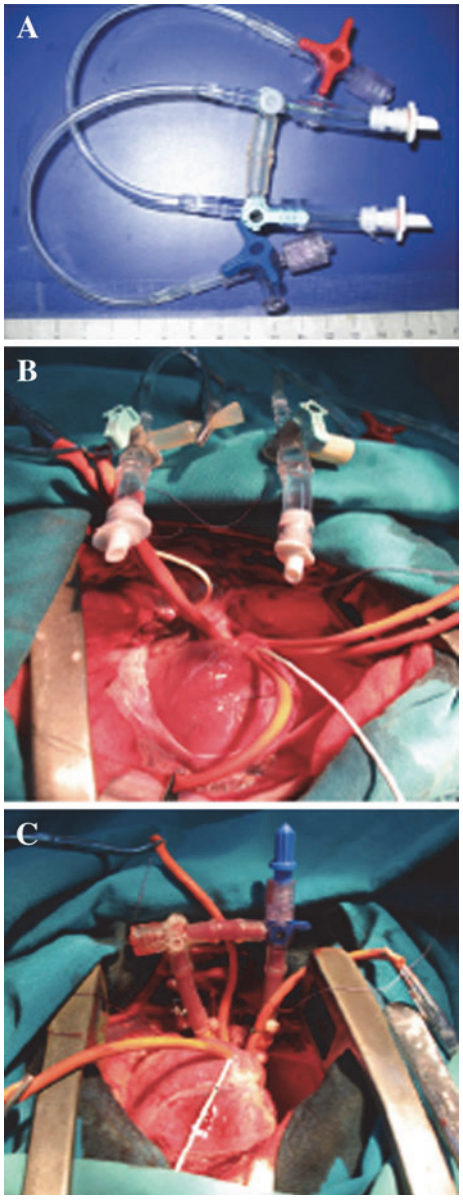

Fig. 2 **a** Aorticopulmonary "U"-shaped external shunt system. Assembled shunt shows two PVC limbs unequally cut to 0.5 cm and connected together with silicone tubing and equipped with two stopcocks and pressure-line connectors. **b** Aorto-pulmonary shunt prefilled with heparinized saline and clamped ready for insertion. **c** Aorto-pulmonary shunt in place with infundibular intrapulmonary artery pressure line (*narrow white tubing*)

Mikro-Tip catheter transducer, Millar) into the right ventricle (RV), through the purse-string suture at the infundibulum, to record RV performance during pulmonary pulsation.

Surgical Procedures

After median sternotomy and pericardiotomy, purse-string sutures (5/0 polypropylene) were positioned at the right atrium (RA) appendage, infundibulum, ascending aorta, and pulmonary trunk.

Cardiac Catheterizations and Hemodynamic Monitoring

A 5F double-lumen central venous line (Hydrocath; BD Technologies) was introduced through the RA purse-string suture for drug administration and RA pressure monitoring. After heparin injection (250 IU/kg), PAP was measured with a 5F Swan-Ganz catheter introduced through the infundibular purse-string suture and pushed forward into the pulmonary trunk. Left atrial (LA) pressure was obtained by direct needle puncture at predetermined time points throughout the experiment. Cardiac output (CO) was measured with a Transonic transit-time flow meter (Transonic) that was temporarily positioned around the aortic root at predetermined time points. Total time (T) of the experiment was 2 h divided into three periods (T1, T2, and T3) corresponding with data collection as follows: T1 = at baseline; T2 = at 1 h after the aorto-pulmonary shunt was turned on, and T3 = at the end of experiment after 1 h of treatment.

Induction of Acute Pulmonary Hypertension

After surgical preparation and data collection for T1, the shunt was prefilled and de-aired with heparinized saline solution and then clamped and separated to facilitate insertion of each limb into the corresponding artery separately. First, the aorta was cannulated, followed by the pulmonary trunk, and then both limbs were connected together. The shunt was de-aired with heparinized saline and turned on for a 1 h period. Animals did not receive any medical support during the first 1 h of shunt operation. Operative details are schematized in Fig. 2 and also shown in the following video: http://www.nourmd.com/.

Therapeutic Phase

After 1 h, the shunt was switched off and removed and the aortic and pulmonary purse-string sutures closed; then hemodynamic data were collected for T2. In group P, the previously inserted Swan-Ganz catheter was replaced by a catheter prototype connected to the ventilator and monitor (Fig. 3). The system was turned on using a constant frequency (110 bpm) irrespective of heart rate (90.6 ± 10.7 bpm). To avoid sudden hypotension, device pulsations were delivered intermittently, interrupted with interval pause according to hemodynamic readings, particularly systemic blood pressure. The global pulsation time was between 10 to 15 minutes and was interrupted by pause time of 5–10 min during a period of 1 h. In group NP, animals were treated with 1 mg/kg phosphodiesterase-5 inhibitor (tadalafil), which was delivered orally through a gastric tube. Animals were then killed using a 10 ml injection of saturated potassium chloride (KCl) at the end of experiment. Pulmonary artery tissues were collected for histopathological analyses.

Hemodynamic Data

Hemodynamic data, including AP, PAP, LA, and RA pressures, heart rate, and CO, were collected from both groups at T1, T2, and T3. The vascular resistance index was calculated using the following formulas:

Pulmonary vascular resistance index (PVRI) = 80* (MPAP−PCWP)/CO*Wt

Systemic vascular resistance index (SVRI) = 80* (MAP−CVP)/CO*Wt where MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge

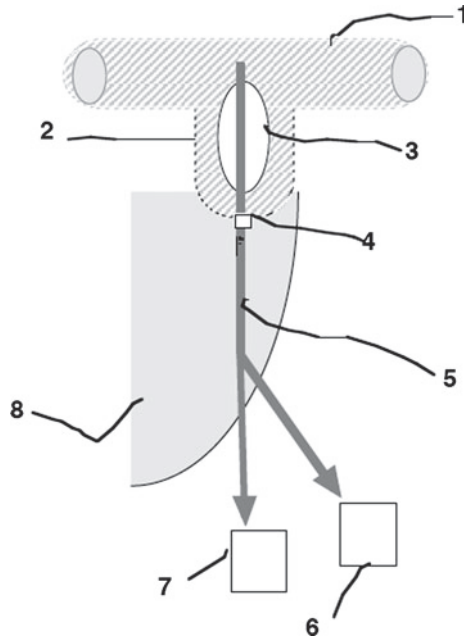

Fig. 3 Intrapulmonary pulsatile system. *1* pulmonary artery branch, *2* pulmonary artery trunk, *3* inflated balloon in place, *4* infudibular snugger, *5* catheter shaft, *6* cardiopulmonary monitor, *7* pulsatile driving system (small animal ventilator), *8* right-ventricular cavity

pressure (substituted for LA pressure); MAP, mean arterial pressure; CVP, central venous pressure (substituted for RA pressure); and Wt, body weight.

Histopathological Investigation

Western Blot Analysis

Western blot analysis was performed, with slight modification, according to Gonzales-Luis et al. [22]. Pulmonary arteries were frozen in liquid nitrogen, stored at −80 °C, and homogenized in a glass potter in 300 ml buffer comprising 10 mM HEPES (Ph 8), 10 mM KCl, 1 mM ethylene diamine tetraacetic acid, 1 mM ethylene glycol tetraacetic acid, 1 mM dithiothreitol, 40 mg/ml aprotinin, 4 mg/ml leupeptin, 4 mg/ml N-alpha-p-tosyl-L-lysine chloromethyl ketone, 5 mM NaF, 10 mM Na2MoO4, 1 mM NaVO4, and 0.5 mM phenylmethanesulfonyl fluoride. The homogenate was centrifuged at 100,000×*g* for 30 min. The supernatant (cytosolic fraction) was collected, and the pellet was resuspended in 200 mL of the same buffer containing nonidet P-40 1 % and gently shaken for 30 min at 4 °C and again centrifuged at 100,000×*g* for 30 min. The pellet was discarded, and the supernatant (particulate-enriched fraction) was collected. The protein content was determined using Bradford assay (reagents from Bio-Rad). Western blotting was performed with 20 mg protein from the cytosolic [for neuronal NOS (nNOS)] or particulate [for endothelial NOS (eNOS)] fractions. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (7.5 % acrylamide) electrophoresis was performed using the method of Laemli in a mini-gel system (Bio-Rad, CA). The proteins were transferred to polyvinyl difluoride membranes overnight, incubated with mouse anti-nNOS (1:1200) or anti-eNOS (1:3000) antibodies (BD Transduction Laboratories) and then with antimouse secondary horseradish peroxidase-conjugated antibody. The bands were visualized by chemiluminiscence (MILLIPORE WBKLS0100; Fisher Scientific) and quantified using image analysis software (TotalLab; Nonlinear Dynamics, UK). The results were expressed as a percentage of the data of newborn animals.

Statistics

Continuous variables are expressed as mean ± SEM. Comparisons between groups of independent samples were performed with Student *t* test for eNOS and two-way analysis of variance for hemodynamic data; $p < 0.05$ was considered statistically significant. GraphPad Prism software was applied for all of the statistical analyses in this study.

Results

Hemodynamic data (Table 1 and Figs. 4, 5, 6) from both groups showed the following:

- T1 to T2: The observed hemodynamic parameters from both groups were nonsignificantly identical. In particular, MPAP was increased after 1 h of aorto-pulmonary shunt from 16.20 ± 2.77 to 33.2 ± 4.66 and from 17.2 ± 3.63 to 36.6 ± 5.7 mmHg in groups P and NP, respectively.
- T2 to T3: In group P, the mean pulmonary arterial pressure (MPAP), was significantly decreased from 33.2 ± 4.66 mmHg at T2 to 9.6 ± 2.97 mmHg at T3 after 1 h of intermittent-period intrapulmonary device pulsations. In group NP, MPAP decreased from 36.6 ± 5.7 mmHg at T2 to 32.2 ± 5.07 mmHg at T3, after 1 h of tadalafil administration. Mean systemic arterial pressure (MAP), decreased significantly in group P from 78.2 ± 21.65 mmHg at T2 to 28.8 ± 11.63 mmHg at T3. In group NP, MAP decreased from 91 ± 14.2 mmHg at T2 to 82.87 ± 15.02 mmHg at T3. Systemic and PVRs (dynes.s.cm^{-5}/kg) decreased significantly in group P: SVRI decreased from 896.4 ± 182.74 at T2 to 298.8 ± 172.85 at T3, and PVRI decreased from 358.2 ± 49.31 to 85.8 ± 42.12 at T3. In contrast to group NP, both systemic and PVRs were increased: SVRI was 1195 ± 566.27 at T2 to 1301 ± 615.79 at T3, and PVRI was 446.8 ± 166.33 at T2 to 478.6 ± 192.91 at T3. In group P, CO at T3 was ± 0.26 versus ± 0.11 (L/min) in group NP. Heart rate (HR), was nonsignificantly decreased in group P: 91 ± 11 bpm at T2 to 69 ± 19 bpm at T3. In group NP, HR was nonsignificantly increased: 84 ± 3 bpm at T2 to 87 ± 14 bpm at T3.

Increased urinary output was observed in all piglets from group P and from none in group NP. eNOS actin manifestation with Western blot test (Fig. 7), was apparently not significant ($p > 0.05$), but it was increased in pulmonary artery segments of group P compared with group NP: 0.81 ± 0.4 versus 0.62 ± 0.2, respectively.

Discussion

This preliminary study proved the feasibility and effectiveness of the intrapulmonary pulsatile catheter as a diagnostic and therapeutic method in acute PAH model. In addition to providing a rapid and significant decrease of PAP and resistances in group P compared with group NP, the study showed some positives points that deserve further analysis. Regarding the importance of the disease, we

Table 1 Summary of hemodynamic results

Variable T1			T2		T3	
	P group	NP group	P group	NP group	P group	NP group
Weight[a]	10.50 ± 0.58[c]	10.6 ± 1.85	ND	ND	ND	ND
HR[a]	83.00 ± 18.93[c]	82.08 ± 17.20	90.6 ± 0.74[c]	84.2 ± 25.52	69.4 ± 19.35[c]	86.6 ± 14.35
MAP (mmHg)[a]	69.00 ± 21.48[c]	73.2 ± 16.78	78.2 ± 21.65[c]	91 ± 14.20	28.8 ± 11.63	82.87 ± 15.02[d]
MPAP (mmHg)[a]	16.20 ± 2.77[c]	17.2 ± 3.63	33.2 ± 4.66[c]	36.6 ± 5.7	9.6 ± 2.97	32.2 ± 5.07[d]
LAP (mmHg)[a]	2.60 ± 0.89[c]	2.7 ± 0.84	4.66 ± 0.96[c]	4.28 ± 1.21	2.56 ± 1.99	4.18 ± 0.86[d]
RAP (mmHg)[a]	2.60 ± 0.55[c]	3.8 ± 0.84	4.8 ± 2.05[c]	5.4 ± 1.52	2.6 ± 1.67[c]	3.54 ± 0.76
CO (L/min)[a]	0.70 ± 0.14[c]	0.8 ± 0.19	0.64 ± 0.15[c]	0.6 ± 0.14	0.56 ± 0.26	0.54 ± 0.11[d]
SVRI (dynes.s.cm^{-5}/kg)[b]	725.80 ± 118.57[c]	677.6 ± 172.04	896.4 ± 182.74[c]	1195 ± 566.27	298.8 ± 172.85	1301 ± 615.79[d]
PVRI (dynes.s.cm^{-5}/kg)[b]	154.80 ± 23.89[c]	152 ± 68.19	358.2 ± 49.31[c]	446.8 ± 166.33	85.8 ± 42.12	478.6 ± 192.91[d]

HR heart rate (bpm)

[a] Measured variable

[b] Calculated variable

[c] $p > 0.05$ between the P and NP groups

[d] $p < 0.05$ between the P and NP groups

would like to draw attention to emerging concepts that may clarify some controversies about PAH management.

Endogenous NO Versus Exogenous NO Donors

Evidence of pulmonary and systemic vasodilatation in group P may be explained by the secretion of a potent vasodilator, such as endogenous NO [23, 24]. To avoid iNO controversies and drawbacks [25], oral tadalafil was applied as an exogenous NO donor and potent pulmonary vasodilator in the NP group [26]. Nevertheless, tadalafil, despite previous successful results in the literature [27], showed fewer impressive outcomes in group NP compared with group P.

Although the advantage of pulsatile therapy compared with the exogenous NO donor was obvious in this study, the real mechanism of the presumed eNOS pathways is still unclear. This hypothesis, i.e., NOS being secreted from the pulmonary endothelium and traveling through the left heart side to affect the systemic circulation, could be opposed by the short biological lifetime of NO [28]. Most probably there must be an undiscovered endothelial mediator(s) and/or mechanism(s) that was triggered by this method. We have similar observations from different studies and models using other pulsatile devices (e.g., suit and tube).

Induced Intrapulmonary Shear Stress

As known, ESS effects could be enhanced by increasing the perpendicular volume expansion (pulse pressure) and/or the tangential friction forces (shear rate). Therefore, delivery of ESS with pulsatile CAD should be induced according to the biophysics and pathophysiological conditions of each heart circuit. For example, under normal hemorheological conditions, microcirculation behavior approaches that of Newton's second law, such as seen in athletics, i.e., a high physical performance (ESS) can be induced by increasing the pulse pressure and slowing the heart rate (shear rate). In contrast, in any abnormal hemorheological state, microcirculation presents behavior that approaches that of Bernoulli's third equation, which is interpreted by the Fahraeus-Lindqvist effect, in which plasma becomes stuck at the inner vascular boundary layers, whereas erythrocytes move faster at the center [29]. This could explain the absence of cyanosis in anemic patients, unlike those patients with high hematocrit, because erythrocyte aggregations at microcirculations induce cyanosis with clinical signs (e.g., clubbed fingers).

Physiologically, the right heart side has specific morphological particularities that must be considered. Contrarily to the left heart side, the right heart side can adjust blood volume and shear rates at five different anatomical zones according to its physiological demands [30]. The PA represents a low-level remodeling zone, similar to systemic veins. At the same time, PA compliance is much greater than that of the large veins [31]. This may explain the controversies over intrapulmonary artery balloon pulsation that arose in the past [32, 33].

Therefore, direct induction of shear stress according to Newton's law, using intravenous (IV) or intrapulmonary pulsatile CAD, must be avoided at the right heart side. Most importantly, delivery of ESS should not disturb the physiological remodeling of the right heart circuit because increased ESS with high pulse pressure promotes serious hemodynamic conditions and irreversible remodeling, such as Eisenmenger syndrome [34, 35] and vein graft disease

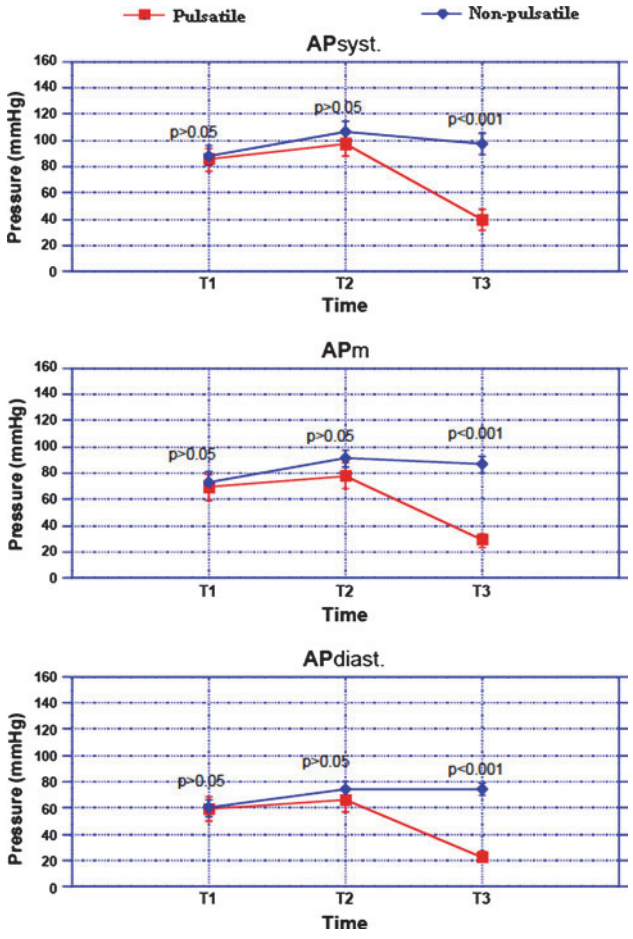

Fig. 4 Systemic arterial pressure. Graphs showing data of systemic arterial blood pressure (AP) obtained from group P (*red*) and group NP (*blue*) at three predetermined time periods: *T1* at baseline, *T2* after 1 h of shunt, and *T3* at end of 1 h of therapy. *APsyst* systolic aortic pressure (*upper panel*), *APm* mean aortic pressure (*middle panel*), *APdiast* diastolic aortic pressure (*lower panel*). AP (mmHg) values were significantly ($p < 0.001$) lower at *T3* in group P compared with group NP

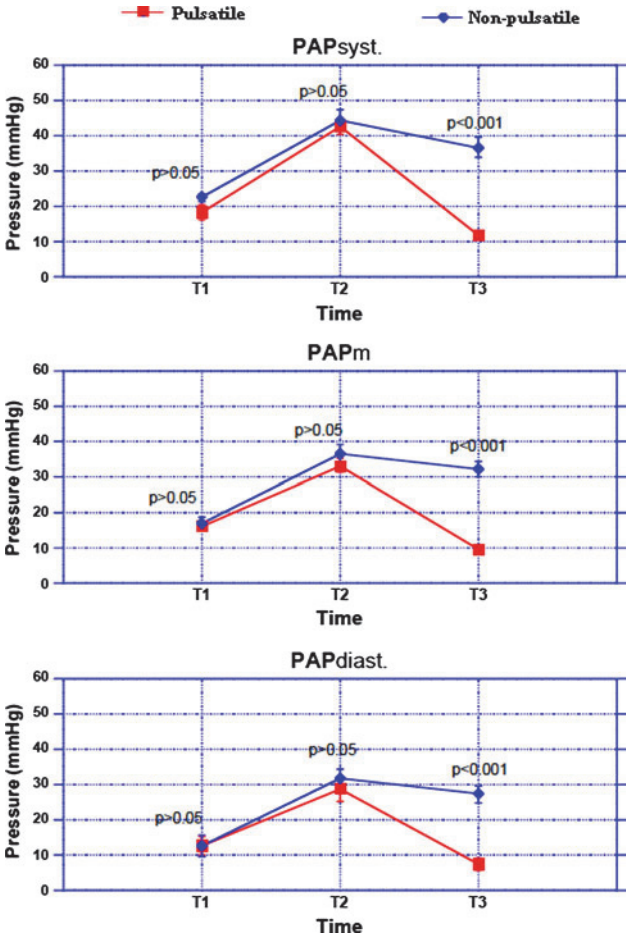

Fig. 5 PAPs. Graphs showing data of PAP values obtained from groups P (*red*) and NP (*blue*) at three predetermined time periods: *T1* baseline, *T2* after 1 h of shunt, and *T3* at end of 1 h of therapy. *PAPsyst* systolic pulmonary pressure (*upper panel*), *PAPm* mean pulmonary pressure (*middle panel*), *PAPdiast* diastolic pulmonary pressure (*lower panel*). PAP (mmHg) values were significantly ($p < 0.001$) lower at *T3* in group P compared with group NP

[36], thus justifying prophylactic procedures, such as PA banding [37].

In our study, we designed a small balloon catheter prototype adapted to the PA trunk. To overrule the compliant PA zone, the catheter was pulsated faster than the heart rate to induce rapid shear rates at the stagnant boundaries' layers of the PA, without volume distension, according to Bernoulli's principles of shear stress [38]. Hopefully, the proposed method may contribute to the prevention of irreversible PAH damage helped by the discovery of new biomarkers [39].

Synchronized Versus Unsynchronized Intrapulmonary Pulsations

Normally, pulsatile cardiac assists devices are synchronized with the diastolic phase at the left heart side to increase coronary flow and improve myocardial ischemia. At the right heart side, and under certain pathological conditions, maintenance of flow dynamics takes priority over the classical diastolic myth. For example, patients subjected to right heart bypass operations survive without and independently to RV diastole [40]. However, in cases of intrapulmonary pulsations with current devices (e.g., IABP), diastolic synchronization must be considered to avoid RVOTO. In this study, we solved the problem of RVOTO with a small-size intrapulmonary balloon catheter. The catheter was pulsated at a greater frequency, irrespective of heart rate, and successfully decreased PAP without obstructing the RVOT. This confirms our therapeutic policy based on similar observations with other pulsatile devices (e.g., suit and tube), proving that pulsatile CAD should not be synchronized with the heartbeat in case of heart failure [41].

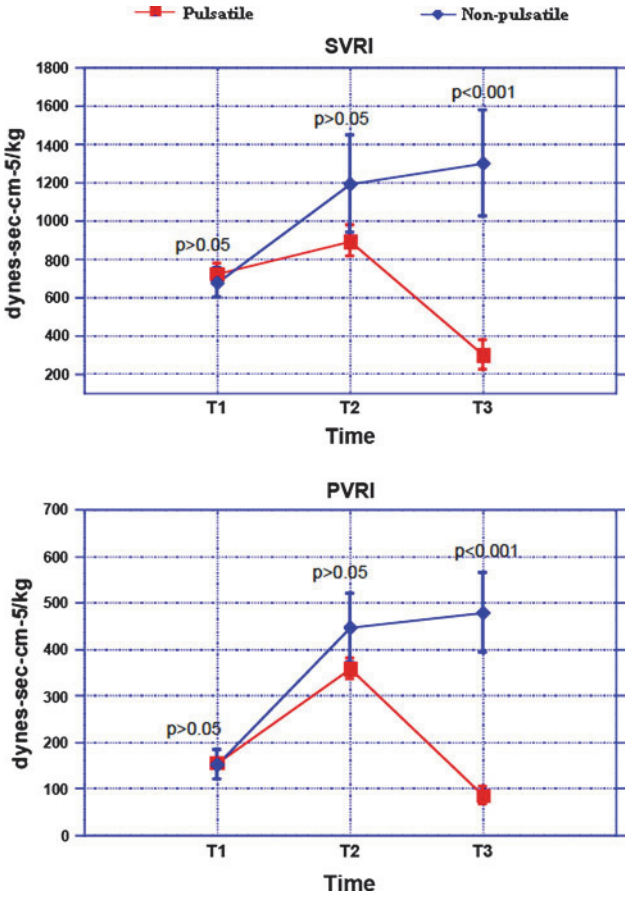

Fig. 6 SVR and PVR indexes. (*Upper panel*) SVRI data calculated from groups P (*red*) and NP (*blue*) at three predetermined time periods: *T1* baseline, *T2* after 1 h of shunt, and *T3* at end of 1 h of therapy. (*Lower panel*) PVRI data calculated from groups P (*red*) and NP (*blue*) at three different time periods: *T1* baseline, *T2* after 1 h of shunt, and *T3* at end of 1 h of therapy. Both SVRI and PVRI (dynes.s.cm^{-5}/kg) were significantly lower ($p < 0.001$) at *T3* in group P compared with group NP

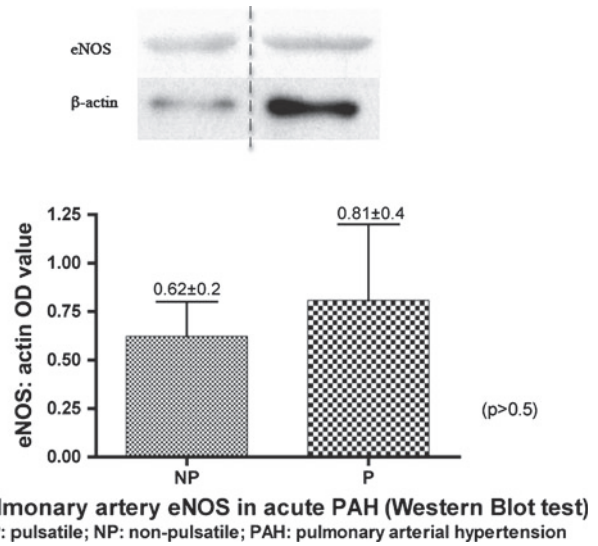

Fig. 7 Pulmonary artery *eNOS* expression using Western blot. *Upper* and *lower panels* show increased eNOS expression in pulmonary artery segments analyzed with Western blot test in group P compared with group NP ($p > 0.05$)

Right Heart Versus Left Heart Endothelium

Contrary to historical consideration of endothelium as a homogenous cell layer, heterogeneity of the pulmonary endothelium is apparent and has been proven in literature from different disciplines [42]. In general, left heart side endothelial functions are most frequently explored and stimulated with devices, such as the IABP, LVAD (e.g. Berlin Heart), pulsatile heart lung machine, etc. In the long-term, these left heart side CAD usually show tolerant effects with further deterioration, rather than restoration, of endothelial function [43].

In contrast, our study results proved the hypersensitivity of the pulmonary endothelium, which is a part of the right heart, to shear stress stimuli. A few minutes of intrapulmonary catheter pulsations were more than enough to decrease a systolic PAP from ≥ 45 mmHg to approximately 9 mmHg within a few minutes (approximately 10), which is contrary to IABP experience at the left heart side. Similar observations were obtained in another model of acute myocardial ischemia treated by the intrapulmonary catheter pulsations [41]. In addition, an external pulsatile trouser, which was tested in an acute RV failure model, successfully decreased RV pressure and PVR, albeit in a slightly longer time frame (approximately 20 min) [44].

Pulmonary Versus Systemic Vascular Resistance

Clinical applications of vasopressors to increase systemic vascular resistance for acute PAH management is currently recommended by intensivists [45]. A similar phenomenon is also observed with tetralogy of Fallot (TOF) cyanotic spells because the patient usually assumes a squatting position to temporarily increase SVR in order to decrease PVR. However, hemodynamically that could be improved physiologically in a TOF patient, whose system may be deteriorated due to vasopressors (e.g., tachyarrhythmia, renal failure, multiple organ failure, etc.) [46].

In this study, the effect of intrapulmonary shear stress enhancement was immediate on both SVR and PVR in group P. Compared with vasopressors, there was evidence of increased renal flow (spontaneous release of a urinary bladder glob) without associated tachyarrhythmia. By the end of the experiment (T3), heart rate was 69 ± 19 bpm in group P compared with 87 ± 14 bpm in the group NP,

which signifies better hemodynamics with less myocardial oxygen consumption.

Animal Model

Current models for PAH are most commonly induced with hypoxia, monocrotaline, and surgical shunts. However, there is still lack of a robust animal model for PAH to guide therapy due to the wide spectrum of changes seen in lung specimens from patients [47].

For example, the absence of intimal proliferation in rat is not similar to the cellular and molecular pathobiology of human PAH [48]. Direct shunt or ligation of one branch of the pulmonary artery do not correlate with the physiopathological conditions of PAH in clinical situations [49]. Another example is the prenatal systemic-to-pulmonary shunt [50], which never functions before birth due to collapsed lungs and low gradient between the systemic (21 % of blood volume) and pulmonary (10 % of blood volume) circulations [51].

Therefore, the study's model was designed according to three prerequisites as follows:

(1) Similar to clinical situations, i.e., induction of acute PAH, such as in the case of a postoperative pulmonary hypertensive crisis [52]. This was achieved successfully with a sizable external aortic-pulmonary shunt circuit.
(2) Sparing of pulmonary endothelial stock, e.g., a temporarily positioned shunt was less traumatic to the pulmonary endothelium compared with current procedures using surgical clamp, stitches, or chemical toxins.
(3) Successful induction of the intrapulmonary shear stress, i.e., a small-size balloon catheter was introduced into the PA trunk.

Nonpharmacological PAH Support Versus Pulsatile Device

The employment of CAD for PAH management is still linked with controversial results [53]. Unfortunately, CAD could aggravate hemodynamics, leading to multiple-organ failure due to factors linked to the devices themselves (e.g., momentum energy losses) or indirectly due to patient-related factors (e.g., age, sex, right or left heart failure, etc.). For example, devices that unload and bypass the left ventricle are less successful when used at the RV, which is preload dependent. It should be emphasized that extracorporeal membrane oxygenation (ECMO) partially deviates some of the venous blood to an external membrane oxygenator [54]. This means ECMO does not unload the RV, and that may explain its successful applications in pediatric patients who are more frequently vulnerable to RV failure.

In contrast, another aspect of the proposed pulsatile catheter therapy is that it could be used as a CAD on its own because a full catheter set (Fig. 1), driven with a small portable or implantable rhythmic generator, could be inserted into the pulmonary trunk for a longer period. This could be achieved intraoperatively through the infundibulum or through a percutaneous IV approach (ongoing study with a chronic hypoxic PAH model).

Most commonly, in acute PAH crises, patients need just few applications to adapt to the newly corrected circulation, such as in case of fenestrated Fontan procedures [55]. Usually, these patients with acute PAH have a PA catheter just for diagnostic purposes. Logically, and according to the study results, an intrapulmonary pulsatile catheter could make procedures, such as fenestrated Fontan, unnecessary and decrease the morbidity and mortality rates of acute PAH.

Study Limitations

Although these results may introduce a valid alternate option for PAH management, some weak points must be improved. This includes the severe systemic vasodilatation encountered at the beginning of our experiments, which was compensated for with IV fluids and intermittent pulsatile periods afterward. A similar phenomenon was observed with nicorandil, an exogenous NO donor used for angina pectoris relief [56]. Meanwhile, vasodilatation that could be induced by exogenous NO donors leads to hypovolemic-cardiogenic shock. In contrast, in the current study, hypovolemia was preceded by general improvement of hemodynamic and organ microcirculation (e.g., increased renal output).

In contrast, this systemic vasodilatation may be explained by several hypotheses as follows: (1) long period of continuous pulsations: (2) unknown endothelial mediator(s) mechanism; and (3) balloon material handmade from commercial rubber, albeit with a slightly large size. We improved this phenomenon in our ongoing study by using new balloon material and a shorter time of intermittent pulsations.

Another study limit was our reliance on hemodynamic data rather than those from large biological investigations. In this study, the collected blood gas samples and respiratory parameters (i.e., CO_2 sensor, ear lobe pulse oximetry) were identical in both groups at baseline (T1), at shunt end (T2), and then became slightly modified by the end of the experiment (T3), most probably due to the short therapeutic period (1 h). Assuming that rapid decrease of PAP, which is usually guided by hemodynamic data in emergency PAH situations, remains our first priority, this was

one reason among others explaining our dependency on hemodynamic as follows: (1) the short therapeutic period (1 h) did not result in a large difference between groups; (2) the shunt flow necessitated adequate CO that could be disturbed with frequent blood samples in a pediatric model; and (3) the high liability of thromboembolic incidence due to external circuit and shunt materials demanded careful shunt care and frequent injection of heparin.

Another study limitation was our late decision to study the traumatic effect of intrapulmonary pulsations on the pulmonary endothelium. Western blot test was performed in four piglets from each group. This may explain why the result was apparently not significantly improved in group P ($p > 0.5$).

Improvements

The study concept deserves further evaluation with larger trials. To overcome the current study limits, we developed a professionally made, new balloon catheter to be used in a percutaneous intravenous pulmonary approach. The device is currently being applied successfully in pigs. A planned chronic hypoxic PAH model will be treated with intermittent periods of catheter pulsations controlled by hemodynamic monitors to maintain PAP at approximately 15 mmHg and will include further in-depth investigations. Group P will be treated without any further support, including mechanical ventilation. The device represents an invasive therapeutic method, which must fulfill patient security and ethical issues as recognized by the United Stated Food and Drug Administration before proceeding to human trials.

Conclusion

An intrapulmonary pulsatile catheter could be used as a diagnostic and therapeutic device for PAH management. Compared with current therapies, the proposed method is cost-effective and would improve morbidity and mortality rates in acute PAH patients, particularly in neonates and pediatric patients.

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Chapitre IX

Publications: Combinaison Pulsatile

Deux articles publiés : Asian Annals of Thoracic and Cardiovascular Surgery (2009 ; 2012).

REVIEW PAPER

The Forgotten Driving Forces in Right Heart Failure: New Concept and Device*

Sayed Nour[1], Guifu Wu[2], Zheng Zhensheng[2], Juan C Chachques[1], Alain Carpentier[1], Didier Payen[3]

[1]*Laboratory of Biosurgical Research, Pompidou Hospital, University of Paris, France*
[2]*Cardiovascular Research Center, The First Affiliated Hospital Sun Yat-sen University, Guangzhou, China*
[3]*Department of Anesthesiology, Critical Care and SAMU, Lariboisiere Hospital, Paris, France*

ABSTRACT

Background: Right heart failure is a frequent hemodynamic disturbance in pediatric cardiac patients. Besides inotropic and chronotropic drugs, fluid administration and inhaled nitric oxide, right ventricular mechanical assistance remains difficult to perform. A circulatory assist device adapted for the right heart biophysics and physiology might be more efficient. **Materials and Methods:** We are developing a prototype of a non-invasive cardiac assist device (CAD) for neonates and pediatrics. It is based on a pulsatile suit device covering and affecting all territories of the right heart circuit. It will be tested in a neonatal animal model of right ventricular (RV) failure. Experimental models will be matched and compared with control and sham groups. Expected results would be immediate hemodynamic improvement due to synchronized diastolic reduction of stagnant venous capacitance, increasing preload and contractility. On long term, increased shear stress with changing intrathoracic pressure in a phasic way would improve and remodel the pulmonary circulation. Future studies will be focused on: hemodynamic, biochemistry, endothelium function test, and angiogenesis. **Comments:** A non-invasive CAD guarantees better hemodynamics and endothelial function preservation with low morbidity and mortality. This is a physiological approach, cost-effective method, and particularly interesting in neonates and pediatrics with RV failure.

(Asian Cardiovasc Thorac Ann 2009;17:525–30)

KEYWORDS: Pulsatile suit, Right heart failure, Shear stress, Pediatric circulatory assist device

INTRODUCTION

Pressurized flow and shear rates are two constant endothelial stimulants that continue to regulate the closed hydraulic cardiovascular circuit since intrauterine life.[1] Our heart and peristaltic arteries represent the main circulatory driving forces, otherwise accessory forces are necessary to move up the steady blood flow at the right heart side.[2]

Surprisingly the right heart could adjust blood volume and shear rates at 5 different anatomical zones according to its physiological demands. In antenatal period, the right heart receives and pumps in equal rates more volume than the left, but keeps low remodeling due to pressure release through physiological shunts.[3] After birth and shunts closure, both right and left ventricles share equal volume and rate inducing equal pulmonary and systemic cardiac output (CO), but remodeling remains inferior at the right heart side most probably due to venous steady flow and ventricular wall trabeculae.

Sayed Nour Tel: +0033140907615 Fax: +0033145405049 E-mail: nourmd@mac.com
Laboratory of Biosurgical Research, 96 rue Didot, 75014 Paris, France.
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According to Guyton concept,[4,5] the venous side blood volume can be considered containing two volumes; first the ''unstressed volume'' that fills the venous circuit without generation of driving flow forces; second, the stress volume that is mobilizing blood towards the right ventricle. Change in partition between these 2 components is physiologically obtained by sympathetic overflow or by fluid loading.[6] The consequence of this partition modification is a change in right heart filling and performance. According to the net effect, this may improve physical performance in healthy persons or cardiac congestion with nitrates in cardiac failure. Although professional scuba divers and astronauts are subjected to totally opposite superficial surrounding pressures, they share almost the same circulatory disorders.[7,8] This may result from a trend to reduce the driving pressure for venous blood, since forward and backward pressures tend to equalize.[9]

In general right ventricular (RV) hemodynamic disorders could be improved by intravenous fluids and chronotropic and inotropic drugs with or without pacemaker.[10] This improvement has potential negative impact such as right side congestion (liver and kidney congestion) and/or reduced right ventricle coronary perfusion during pacing.

Conversely to adult context, right heart failure occurs more frequently in pediatric patients with more endothelium dysfunction than atherosclerosis.[11] As a consequence, left heart cardiac assist devices as intra-aortic balloon pump cannot be efficient because of the large vessel compliance in pediatric patients.

The aim of this work is to develop a non-invasive cardiac assist device (CAD) to improve or replace accessory driving forces, adjust the requested volume and rates in each zone of the right heart circuit in regular synchronized pulsations. Leading to a better hemodynamic as well as remodeling specially in the very young populations.

Concept and Device

Understanding volume and rate interdependency mechanism is the main concept of this study for building up the best device adapted to the right heart physiology and biophysics. As shown in (Table 1) and (Figure 1) we could distinguish 5 different anatomical zones:

Zone1: low remodeling systemic venous zone, where blood is driven from extremities helped by the aforementioned accessory driving forces in a low pressure, steady stream flow.

Zone 2: mild remodeling atrio-ventricular cavity zone, where the tangential frictions wall stress is induced by contractions are tamed and alleviated by trabeculae in order to keep the right ventricular mass almost the $1/6^{th}$ of the left one.[12]

Zone 3: normal remodeling zone, represented by the interventricular septum.[13]

Zone 4: high remodeling infudibular zone.

Zone 5: low remodeling zone of the pulmonary arterial tributaries, with low resistance and pressure as shear forces are already alleviated due to trabeculae, rotation and squeezing axis of the RV, infudibulum, the pulmonary artery compliance capacity, competent valves and less developed Valsalva.

Device design: A 3 layers, pulsatile suit composed of detachable parts: a. trouser, b. waist belt, c. chest jacket. The three parts will be reassembled together in one unit and wrapped tightly around the patient body through straps and zippers, as shown in (Figure 2) and as patent descriptions (WO/2008/000111).

The suit would be connected to a generator of rhythmic driving force, through specific connectors. Regular pulsations would be obtained via a currently used pneumatic driving forces, or a specific either pneumatic or low voltage-electric system.

The suit must be suitable for the postoperative situations and provided with security features as following:

1. Inner layer made of elastic material (e.g. neoprene) to insure smooth tight massage like pulsed surge at the baby's delicate skin.
2. Middle sandwiched layer filled with gelatinous fluid, to alleviate the vigorous inflation/deflation, power induced by the driving force.
3. External layer made from tougher materials to keep the pulsed wave inwards toward the body. This part is equipped by security air releasing valve to prevent over inflation accident in case of mechanic defect.
4. Holes are previewed in the suit body, in order to facilitate medical administrations and prevent bedsores.
5. Layers thickness and design are modified according to age, body weight and indication of the patient.
6. The back portion of the trunk part of the suit (vest and belt) must not be inflatable in order to avoid any spinal, or back injuries.
7. Blood must be pulsed back from periphery towards the heart in a sloping progressive wave in longitudinal axis. Except at the chest part, pulsations must be started backward - forward towards the front, in a horizontal axis in such a manner to increase venous return within respect of the respiratory movement.

Table 1. **Right heart postnatal remodeling zones**

Zones	Anatomical site	Remodeling	Main Factors
Z1	SVC, IVC	Low	Accessory Driving forces → Steady flow
Z2	A-V cavity	Mild	Trabeculae
Z3	Septum	Normal	–
Z4	Infundibulum	High	↑ Coronary supply
Z5	PA tributary	Low	↓Pressure, Pulmonary Valve + Infundibulum

Z = zone, SVC = superior vena cava, IVC = inferior vena cava, A-V = atrio-ventricular cavity; RV = right ventricle; PA = pulmonary artery.

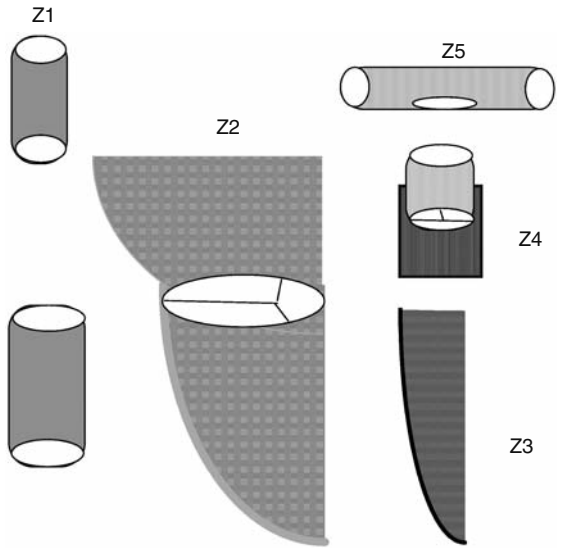

Figure 1. Represents the 5 different remodeling zones of the right heart circuit as following: • Zone 1 (Z1) represents the superior vena cava (SVC) and inferior vena cava (IVC) low remodeling zone. • Zone 2 (Z2) represents a mild remodeling zone of the right atrio-ventricular cavity (A-V cavity). • Zone 3 (Z3) represents a normal remodeling interventricular septum zone. • Zone 4 (Z4) represents high remodeling infundibular zone. • Zone 5 (Z5) represents a pulmonary artery low remodeling zone.

8. Device manipulation including pulse rate, inflation volume . . . etc must be adapted to each clinical situations to insure a harmonic, homogenous venous return waveform, in continuity with each part.
9. The chest jacket and sleeves must be synchronized together in a manner to avoid respiratory distress or vascular incidents at the armpit, e.g. thrombosis, edema.
10. Each suit component has its own inflation/deflation control security valve. This allows different pressure application according to different parts of the delicate pediatric body.

Models: a neonatal animal model of right ventricular (RV) failure. Future studies will be focused on: hemodynamic, biochemistry, endothelium function test, and angiogenesis. Experimental models will be matched and compared with control and sham groups.

Patients: The suit could be applied in clinical trials, in patients with chronic RV failure after right heart bypass operations as secured non-invasive device.

Expected results: would be immediate hemodynamic improvement due to synchronized diastolic reduction of stagnant venous capacitance, increasing RV preload and contractility. On long term increased shear stress with changing intrathoracic pressure in a phasic way would improve and remodel the pulmonary circulation.

Discussion

The pulsatile suit could assist or replace some of the troubled accessory driving forces and factors (Table 2), that affect the right heart circuit.[14] A tight elastic suit driven by regular external synchronized pulsations could induce a continuous harmonic compressive waveform movement over the body. This blood movement is obtained by squeezing stagnant venous capacitance which is usually accumulated at the superficial venous - lymphatic vessels and visceral area in infants. The consequence for right heart would be a better filling inducing a better function to push blood towards pulmonary circulation. In addition, this principle could increase vascular shear stress in pulmonary circulation which has been described as an important controller of the downstream vascular resistances.[15]

The potential effect of the device on the different defined anatomical zones can be viewed as follows (Table 3): Increased volume in zone ''1'' induces venous circuit hemodynamic disorders with a venous congestion, reduction of such a congestion is a major goal for treatment. To achieve it, one can use diuretics, increase in venous capacitance by nitrates and improve in right ventricular pumping by inotropic-chronotropic drugs.

This strategy may have side effects such as a non adapted reduction of preload, increase myocardial oxygen consumption related to tachycardia, and arterial blood pressure fall.

The proposed device would improve the mobilization of the venous congestive blood towards the pulmonary

circulation synchronized or not with the right heart rhythm, in a more physiological way. It keeps the optimal preload, does not increase the heart rate, and reduced the venous congestion.

In addition, for the zone 2 and 3 for which the diastole is essential, the device may help to oxygenate the trabeculated crypts and the ventricular septum coronary circulation particularly in complex congenital heart disease.[20] In zone 4 and 5, both volume and rate are needed to keep pulmonary resistance as low as possible in acute situation. A sustained better volume put the pulmonary circulation in a condition of remodeling. If such a remodeling is over efficient in absence of endothelial function, it might induce pulmonary vascular hypertrophy leading at maximum to an Eisenmenger syndrome.[16] The proposed device might overcome such inconvenience by decreasing pulmonary afterload through endogenous nitric oxide process and enhancement of ventricular mass remodeling, particularly in patients of sub-acute and chronic pulmonary hypertension.

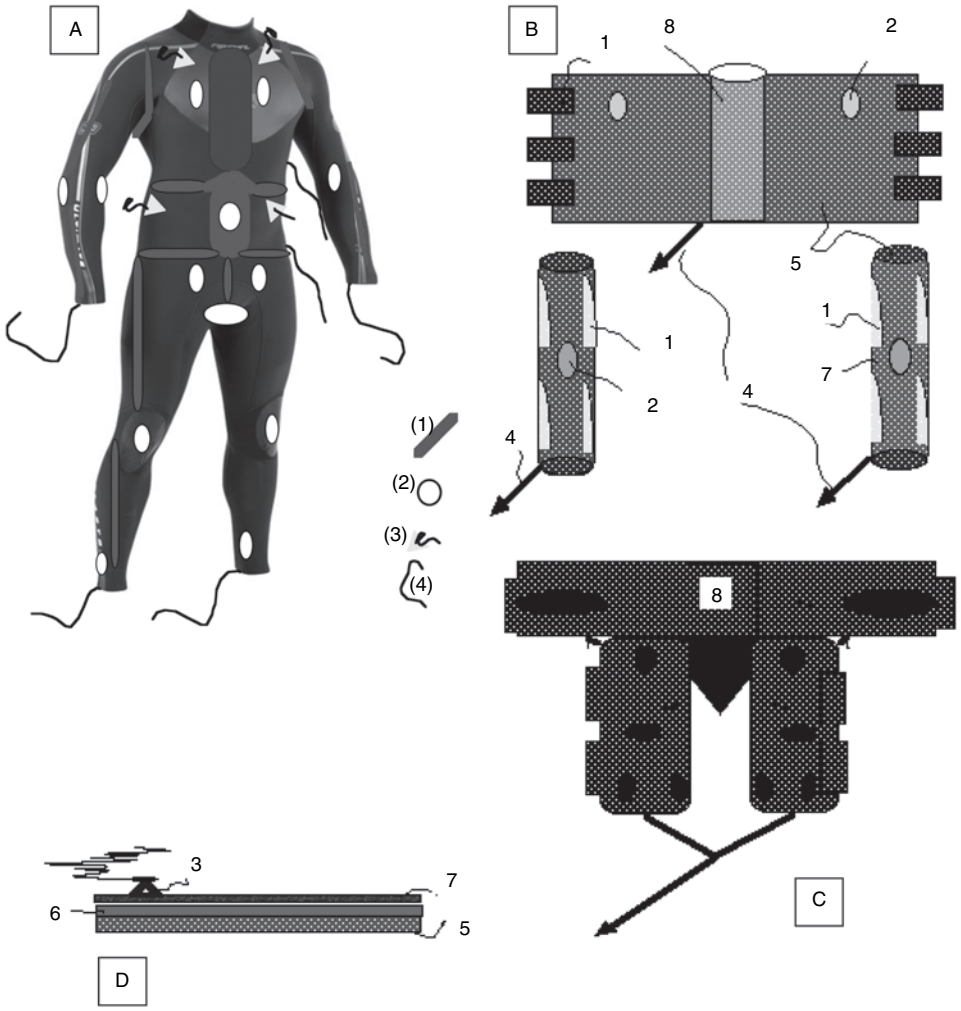

Figure 2. Shows 4 schematic figures (A,B,C and D) of the pulsatile suit cardiac assist device (CAD): • (**A**), represents a whole figure of the pulsatile suit in 3 units compartments (jacket, belt and trouser), reassembled together and detailed as following: 1 = Zipper and straps, are conceived to keep the suit tightly fit to the body. 2 = Holes, to allow body access for medical management. 3 = Security air release valve, to avoid over inflation accidents in case of mechanical failure. 4 = Airport connectors, adapted to pneumatic rhythmic driving force. 5 = Inner layer in direct contact with the skin, made of elastic material (e.g. neoprene). 6 = Sandwiched, middle layer, contains gelatinous fluid, allowing mitigation of pulsed shocks, and facilitating impulses propagation. 7 = Air receiving external space, connected directly to pneumatic driving force, through airports (4), and security valves (3), to allow air delivery inward-towards the body in safe manner. 8 = Non-inflatable parts at the posterior parts of the suit to avoid spinal injury. • (**B**) = Represents the supra-diaphragmatic compartment of the suit, means a Jacket, composed of vest and 2 sleeves, that could be reassembled together through zippers and straps to fit the patient body tightly and securely to be used as circulatory as well as respiratory assist. • (**C**) = Trouser and waist Belt, representing the infra-diaphragmatic compartment of the suit. • (**D**) = Shows the 3 suit layers: (5–7) arranged inward-outward respectively, with air release security valve[3] attached to the external layer[7].

The previous systems used for management circulatory disorders such as anti-G suit[17] cannot be used in pediatric context. Cardiomyoplasty as bioassist device,[18] which was used in RV failure by increasing shearing rate only in volume dependent zone 2 and 3, might not be efficient for right heart bypassed patients. The other devices (Table 4), such as enhanced external counter-pulsation (EECP)[19] are mostly indicated and usable for adults and do not fit well with pediatric patients. They induce strong and vigorous compression forces on deep arteries and on thoracic cage, which may have side effects in the pediatric patients.

Concerning clinical application of this concept and device, it is important to remark that this is the first described ''non-invasive cardiac assist device'' for neonates and pediatrics. It will be equipped with security features facilitating clinical use, e.g.: in cases of failed Fontan procedure with no issues except heart transplant.

Table 2. **Postnatal accessory driving forces and factors**

Venous driving pump
Muscle pump
Thoracic pump (Respiratory muscles, Diaphragm)
Gravity
Atmospheric pressure
Pericardium
Venous valves
Oncotic pressure
Skin Baroreceptors

It is important to consider the right heart compliance in physiological conditions (represented by Z1 in our concept). Since the right heart circuit contains almost 64% of blood volume, i.e. venous compliance is 10–20 times greater than systemic arterial compliance, therefore the right heart represents a compliant chamber and a good candidate for positive remodeling.[21] A decreased pulmonary vascular resistance is the mean target in any case of right heart hemodynamic disturbances, which is shear stress-mediated endothelial nitric oxide synthesis (NOS) dependent. Clinically in acute RV failure, the improvement of hemodynamics with chronotropic drugs or pacemaker is directly related to increased pulmonary shear rates. Except our proposed pulsate suit, nothing is currently available for the chronic phase of RV failure management.

Proven clinical evidences show that the RV is a preload dependent ventricle, necessitating both systolic and diastolic phases for its oxygenation. RV is seriously jeopardized in cases of decreased venous return, for this reason is highly recommended to avoid nitrates in RV ischemia. Recently it was shown improved Norwood's operation results with the Sano's shunt, due to increased RV diastolic filling. Maintained RV volume by IV fluids

Table 3. **Pulsatile suit expected beneficial patients groups**

Zones	Mechanism	Patients groups*
Z1	↓venous capacitance, ↑ shear rates	RV bypass, Fontan operation, Orthostatic intolerance syndrome, ED syndrome, Divers, Astronauts, ...
Z2	↑Preload, ↑ shear rates, ↑ angiogenesis	TOF, Norwood
Z3	↑ Preload, ↑ angiogenesis	RV coronary dependent
Z4	↓ afterload, ↑ angiogenesis	RVPA transannular patch
Z5	↓ afterload, ↑ angiogenesis	Acute, chronic PHT

*Symbolic Categories, Z = zone, RV: right ventricle, TOF: Tetralogy of Fallot, RVPA: right ventricle-pulmonary artery; PHT: pulmonary hypertension, ED: erectile dysfunction.

Table 4. **Pneumatic Circulatory Assist Devices**

Device	Functions	Patent n°
Pneumatic Vest	Cardiopulmonary resuscitation	WO 96/28129[1]
Pneumatic Vest	Respiratory assist	US6676614B1[2]
Pulsatile cuffs	Circulatory assist	US19970955421[3]

[1]Mark G, George GK, Henry H. Improved vest design for cardiopulmonary resuscitation system. University Johns Hopkins (US), Card Systems INC (US). 1996-09-19. [2]Craig H, Lonnie H. Vest for body pulsating method and apparatus. Electromed INC (US); 2004-01-13. [3]Zhensheng Zh, Zhili H, Shifang Y. High efficiency external counterpulsation apparatus and method for controlling same. Vasomedical INC (US) 1999-12-07.

is mandatory in cases of RV failure. Otherwise it is true that vigorous abrupt squeezing forces could deteriorate the overloaded RV, for this reason the device is equipped with security features, as been detailed, to insure sloping smooth regularly synchronized pulsed waves at the level of the superficial venous system.

We believe that this concept is a cornerstone approach in RH failure management. Currently we are testing prototypes in neonate piglet's models with acute pulmonary hypertension (Z5) and acute RV failure (Z2). Future studies will include application of this concept in chronic or sub-acute phase of right heart failure models, which are usually affecting (Z1).

Conclusion

A pulsatile suit is a physiological, non invasive therapeutic method to manipulate the right heart side natural blood reservoir containing almost 64% the total blood volume and endothelium stores. Such a reservoir serves as a physiological therapeutic backup in case of hemodynamic disturbances and circulatory disorders particularly in pediatrics.

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Original Article

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SAGE

Forgotten driving forces in right heart failure (Part II): experimental study

Sayed Nour[1,2], Gang Dai[2], Qinmei Wang[2], Fei Wang[2], Juan Carlos Chachques[1] and Guifu Wu[2]

Abstract

Background: Cardiac-assist devices for right ventricular failure remain controversial with poor results. This study evaluated a pulsatile cardiac-assist device in an acute right ventricular failure model vs. current therapies.

Materials and methods: Pulmonary regurgitation was created in 12 piglets by valve avulsion and external transfixation of 2 pulmonary artery cusps suspended to the pulmonary arterial wall. The piglets were divided into 2 treatment groups: a pulsatile group P and a non-pulsatile group NP. Management started when severe right ventricular failure was observed (48.1 ± 24.5 min). In group P, pulsatile trousers driven by a pneumatic generator were pulsated intermittently at 40 beats·min^{-1}. Group NP was treated with oral tadalafil 1 mg·kg^{-1}, intravenous fluids, and adrenaline 0.3 μg·kg^{-1}. After 1 h of therapy, cardiac output was significantly better in group P than group NP (1 ± 0.2 vs. 0.7 ± 0.2 L·min^{-1}). Mean right ventricular pressure (16 ± 6 vs. 24 ± 2 mm Hg) and pulmonary arterial pressure (22 ± 1 vs. 31 ± 2 mm Hg) were lower in group P. Vascular resistances indices were lower in group P than group NP: pulmonary resistance index was 174 ± 60 vs. 352 ± 118 dyne·sec·cm^{-5}·kg^{-1}; systemic resistance index was 611 ± 70 vs. 1215 ± 315 dyne·sec·cm^{-5}·kg^{-1}. Western-blot analysis showed higher endogenous NO synthase expression in group P pulmonary arteries.

Conclusions: The pulsatile suit can be used safely as a noninvasive cardiac-assist device in acute right ventricular failure. This represents a cost-effective nearly physiological method, suitable for adults and children.

Keywords

equipment design heart-assist devices, hemodynamics, pulsatile flow, ventricular function right

Introduction

Right ventricular (RV) failure is an endothelial dysfunction disease caused by disturbed flow dynamics due to pump failure and/or elevated pulmonary vascular resistance.[1] Clinically, RV failure in an acute or acute-on-chronic presentation may predispose to hemodynamic shock and multiple organ failure, with high mortality.[2] Current strategies for management of RV failure can be summarized as based on 3 principles: reduction of afterload with pulmonary vasodilators, increasing preload with intravenous fluids, and increasing contractility with chronotropic drugs or a pacemaker. Additional hemodynamic assessments may be needed with the employment of cardiac-assist devices (CAD) and/or surgical procedures such as a Blalock-Taussig shunt, an RV bypass operation, and heart transplantation as the ultimate means of management.[3,4] Unfortunately, results of RV-assist devices (RVAD) are still controversial and uncertain.[5] As most of the current RVAD are functionally simulating, those applied for left ventricular support are mainly designed to unload and divert stroke volume from a failed left ventricle towards the aorta, whereas RV hemodynamics are preload dependent and could be seriously disturbed by ventricular discharge. In addition, a low-pressure and highly compliant pulmonary

[1]Laboratory of Biosurgical Research, Pompidou Hospital, University Paris Descartes, Paris, France
[2]Division of Cardiology and the Key Laboratory on Assisted Circulation, Ministry of Health of China, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Corresponding author:
Sayed Nour, Laboratory of Biosurgical Research, Pompidou Hospital, University Paris Descartes, 56 rue Leblanc, 75015 Paris, France
Email: nourmd@mac.com

artery would not be biophysically perfused in the same manner as the aorta.[6] Furthermore, RV failure is more frequent in children where size matters, as most CAD were initially designed for adults and are more suitable for bigger body surface areas.[7] It should be emphasized that extracorporeal membrane oxygenation deviates part of the venous blood to an external membrane oxygenator.[8] This means that extracorporeal membrane oxygenation does not unload the RV, and this may explain its successful application in pediatric cases, despite the severe associated energy momentum loss. Alternatively, following our previous study, we have investigated a pulsatile suit for therapy in an acute RV failure animal model.[1]

In this study, a prototype of pulsatile trousers and belt was tested in piglets with acute RV failure, and the results were compared to those of a control group managed with traditional pharmacological therapies. The expected hemodynamic improvement should occur due to shear stress-mediated enhancement of endothelial function, stimulated by trouser pulsations on the stagnant infradiaphragmatic venous capacitance.

Materials and methods

As described previously, the pulsatile suit is a noninvasive CAD composed of 3 layered compartments: an inner elastic layer (neoprene), an intermediate layer that contains gelatinous fluid (glycerin), and an external air chamber layer connected to a pneumatic rhythmic generator.[1] The suit is designed to cover a portion of the human body, and the therapist (doctor, nurse, or even patient) can put in place without effort. The suit may be connected directly to an external pump, as shown in Figure 1A. This pulsatile suit may take on various forms such as a hood, a pair of trousers, a jacket, a glove, a boot, or a sock. The structure serves to guide the pulsations progressively in the direction of venous return, thus constituting a CAD for the RV. For more details, please refer to Figure 1 and patent descriptions: WO/2008/000110, US2009/203956, and WO2010/070018. The pulsatile trousers designed for neonate piglets (Figure 1B) was wrapped around the piglet trunk in a reverse manner (Figure 1C), and kept loose on standby. The pneumatic driving force was an EECP MC-2 pneumatic generator (Hua Wen Medical Equipment Co. Ltd., Fo-Shan, China).

This study was approved by the Animal Research Facility at Sun Yat-Sen University and conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No.85-23, revised in 1996). Twelve domestic piglets of both sexes were randomly designated to either the pulsatile group P ($n = 6$; 10.50 ± 0.58 kg) or the nonpulsatile group NP ($n = 6$; 10.6 ± 1.85 kg). Animals were premedicated intramuscularly with 3 mL of an anesthetic mixture composed of dihydroetorphine hydrochloride, dimethylaniline thiazole, ethylenediaminetetraacetic acid, haloperidol (Su-Mian-Xin), and midazolam $0.5\,mg{\cdot}kg^{-1}$. The animals were placed on a warmed operating table and monitored with a rectal probe. Anesthesia was induced and maintained with 3% sodium phenobarbital ($mg{\cdot}kg^{-1}$) injected through a peripheral venous line. After a median cervicotomy and tracheotomy, a 3.5-5 tracheal tube was inserted, followed by mechanical ventilation (PA-500; PuLang Technologies, Inc.) with 40% oxygen and a tidal volume of $10–15\,mL{\cdot}kg^{-1}{\cdot}min^{-1}$ and respiration frequency of 15 breaths per minute. The right carotid artery was isolated and cannulated with a 6F arterial sheath. A 4F Millar probe (Mikro-Tip Catheter Transducer; Millar Instruments) was introduced through the carotid line into the aorta for continuous systemic arterial pressure (AP) monitoring (Biopac physiology monitoring system); this enabled the other hemodynamic measurements described below.

After a median sternotomy, pericardiotomy, and dissection of the great vessels, pursestring 5/0 polypropylene sutures were positioned at the right atrial (RA) appendage and infundibulum. A 5F double-lumen central venous line (Hydrocath; B-D Tech.) was introduced through the RA pursestring for drug administration and RA pressure monitoring. After a heparin injection ($150\,IU{\cdot}kg^{-1}$), a 5F Swan-Ganz catheter was introduced through the infundibular pursestring and pushed forward into the pulmonary trunk. Another Millar catheter (3F Mikro-Tip) was introduced into the RV through the pursestring at the infundibulum, and guided towards the ventricular cavity for RV pressure (RVP) recording. Left atrial (LA) pressure was obtained by direct needle puncture at predetermined time points throughout the experiment. Cardiac output (CO) was measured with a transit-time flowmeter (Transonic Systems, Inc.) temporarily positioned around the aortic root at predetermined times. The vascular resistance indices were calculated with the following formulae:

$$\text{Pulmonary vascular resistance index (PVRI)} = 80 \times (\text{MPAP} - \text{LA})/\text{CO} \times \text{body weight}$$

$$\text{Systemic vascular resistance index (SVRI)} = 80 \times (\text{MAP} - \text{RAP})/\text{CO} \times \text{body weight}$$

Where CO = cardiac output, CVP = central venous pressure, (substituted for RA pressure), MAP = mean arterial pressure, MPAP = mean pulmonary arterial pressure, and PCWP = pulmonary capillary wedge pressure (substituted for LA pressure). The RV

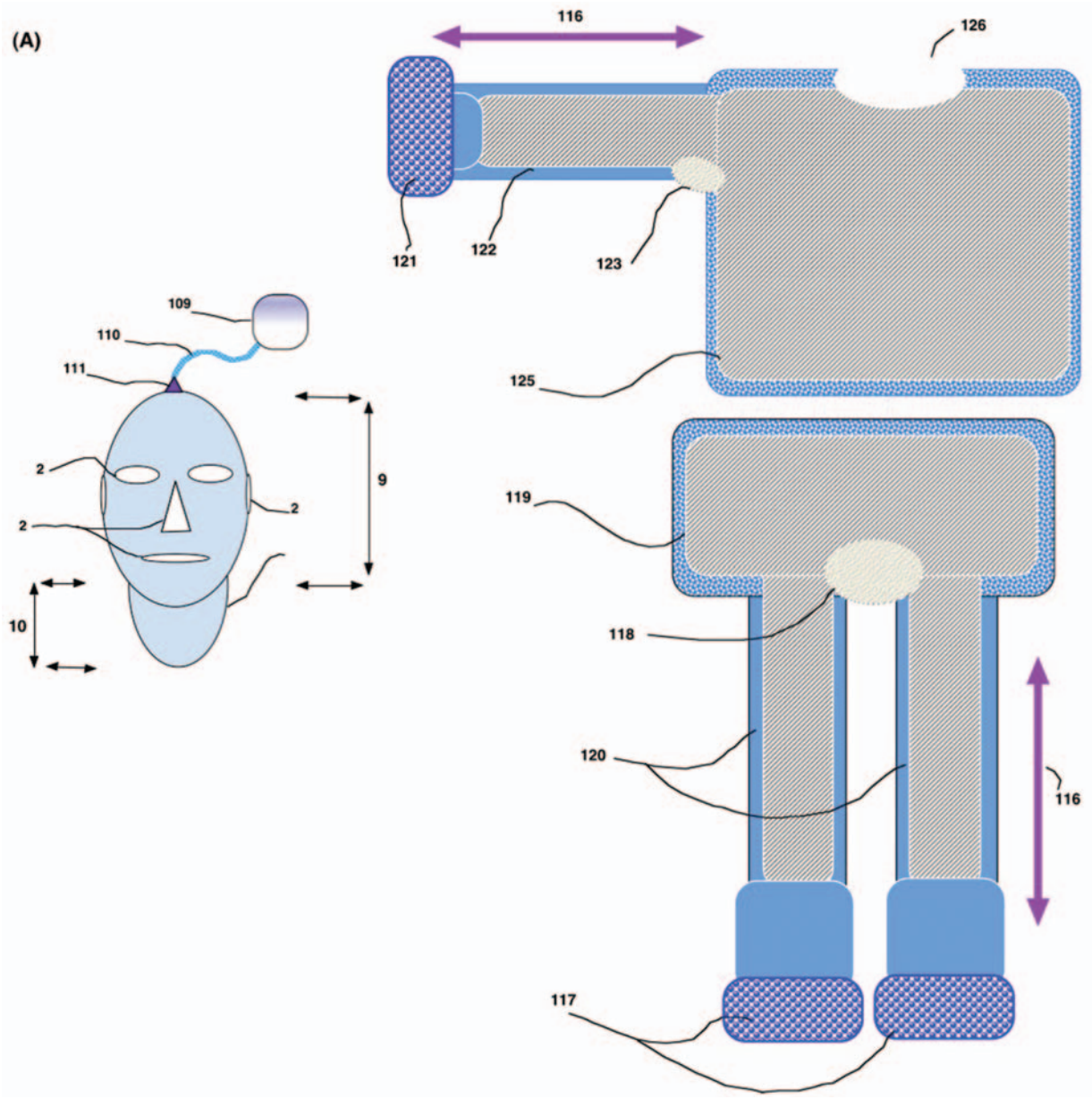

Figure 1. (A) Schema of the patented Pulsatile Suite II. Upper right panel shows the pulsatile jacket composed of a vest (125), sleeve (122), and integrated gloves (121). Lower right panel shows pulsatile trousers (120) with integrated belt (119) and boots (117). Left panel (A) shows a pulsatile mask with holes (2) for ears, eyes, mouth and nose. A pulsatile generator (109) is attached to the mask with a connector system (110, 111). Arrows represent the main axes of venous return for the trousers and jacket (116) and mask (9, 10). (B) Pulsatile trouser prototype for piglets, showing the non-pulsatile frontal zone. (C) Intraoperative view of the pulsatile trousers. The trousers were wrapped to pulsate the hepatic capacitance rather than the dorsal region. Additional pulsatile cuffs were positioned at the lower limbs. (D) Intraoperative view in one piglet from group P. Left panel shows the bulged dyskinetic RV free wall after acute pulmonary regurgitation. Right panel shows the decreased bulged zone after trouser pulsations. Blue arrows indicate the anterior interventricular sulcus before (left) and after (right) trouser pulsations.

coronary driving pressure was calculated as mean AP – mean RVP.[9]

The total time of the experiment was 2 h, divided into: baseline (T1), approximately 1 h after creation of acute RV failure (when severe RV failure was observed) and before starting the treatment (T2), and after 1 h of treatment (T3). For induction of acute RV failure, acute pulmonary regurgitation was created by pulmonary valve avulsion using an intra-infundibular balloon catheter, then changed to a less aggressive technique: 2 accessible PA cusps (the right facing and non-facing cusps) were externally transfixed and suspended to the PA wall with 4/0 polypropylene stitches. Pulmonary incompetence was confirmed and evaluated by vascular

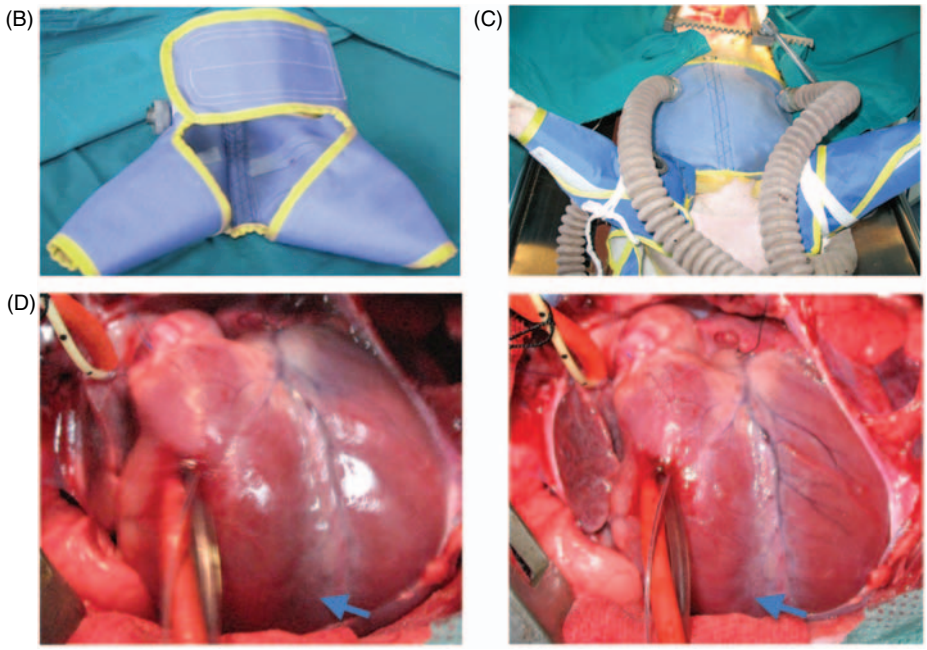

Figure 1. Continued.

Doppler ultrasound (Smartdop 5O EX-F; Koven Technology, Inc. St. Louis, MO, USA). Operative details are shown in the following videos: https://www.me.com/gallery/#100050 and https://www.me.com/gallery/#100063 for group P, and https://www.me.com/gallery/#100053 for group NP. The animals received no treatment after induction of RV failure and during the whole period of T2. Hemodynamic deterioration was determined macroscopically by the severely expanded RV free wall; the total T2 period was 48.1 ± 24.5 min, and T3 was after 1 h of treatment.

In group P, the prototype trousers were wrapped around the abdomen and inferior limbs of the piglets before sternotomy, and kept loose on standby. At the end of T2, the trousers were tightened and the pneumatic generator was switched on at a fixed frequency of 40 cycles/min irrespective of heart rate, and a moderate inflation/deflation pressure (<0.8 bar). Pulsations were delivered intermittently, interrupted with a pause according to the hemodynamic and respiratory parameters. The total pulsation time was 15–20 min over 1 h. In group NP, a phosphodiesterase type 5 inhibitor (tadalafil 1 $mg \cdot kg^{-1}$) was given orally through a gastric tube, as well as intravenous adrenaline 0.3 $\mu g \cdot kg^{-1}$ and fluid (Plasmion). Hemodynamic data were collected from both groups at T1, T2, and T3, including AP, pulmonary artery pressure (PAP), LA and RA pressures, heart rate, and CO. The animals were euthanized by injection of 10 mL of saturated potassium chloride solution at the end of the experiment. Pulmonary artery tissues were collected for histopathological analyses.

The Western blot test was performed with a slight modification to the protocol as follows:[10] the pulmonary arteries were frozen in liquid nitrogen and stored at −80°C until use. They were homogenized with a glass pestle in 300 mL of a buffer composed of: 10 mM HEPES (pH 8), 10 mM KCl, 1 mM ethylenediaminetetraacetic acid, 1 mM ethylene glycol tetraacetic acid, 1 mM dithiothreitol, 40 $mg \cdot mL^{-1}$ aprotinin, 4 $mg \cdot mL^{-1}$ leupeptin, 4 $mg \cdot mL^{-1}$ N-alpha-p-tosyl-L-lysine chloromethyl ketone, 5 mM NaF, 10 mM Na_2MoO_4, 1 mM $NaVO_4$, and 0.5 mM phenylmethane-sulfonyl fluoride. The homogenate was centrifuged at 100,000 *g* for 30 min. The supernatant (cytosolic fraction) was collected, and the pellet was re-suspended in 200 mL of the same buffer containing 1% Nonidet P-40, gently shaken for 30 min at 4°C, and centrifuged again at 100,000 *g* for 30 min. The pellet was discarded, and the supernatant was collected (particulate-enriched fraction). The protein content was determined using the Bradford assay (reagents from Bio-Rad). Western blotting was performed with 20 mg of protein from the cytosolic fraction for neuronal nitric oxide synthase (nNOS) and from the particulate fraction for endothelial nitric oxide synthase (eNOS). SDS-PAGE (7.5% acrylamide) electrophoresis was carried out using the Laemli method in a mini-gel system (Bio-Rad, CA, USA). The proteins were transferred to polyvinylidene fluoride membranes overnight, incubated with mouse anti-nNOS (1:1200) or anti-eNOS (1:3000) antibodies (BD Transduction Laboratories) and then with anti-mouse secondary horseradish peroxidase-conjugated antibody. The bands were visualized

by chemiluminescence (Millipore WBKLS0100) and quantified using image analysis software (TotalLab, Nonlinear dynamics, UK).

Continuous variables are expressed as the mean ± standard error of the mean. Comparisons between groups of independent samples were performed with the Student t test for eNOS and a 2-way analysis of variance for hemodynamic data. A p value less than 0.05 was considered statistically significant. GraphPad Prism software was applied for all the statistical analyses in this study.

Results

There was evidence of acute RV failure in both groups after the creation of severe PA regurgitation. This was confirmed by Doppler echo studies. Macroscopically, a bulging dyskinetic zone of the RV free wall appeared in all animals (Figure 1D). Hemodynamic data at the 3 time points are summarized in Table 1. Compared to the baseline (T1), there were similar degrees of elevated RVP, PAP, SVRI, PVRI, and CO deterioration at the end of T2 in both groups. At the end of experiment (T3), all the piglets in group P had survived, but there were only 4 survivors in group NP. The dyskinetic zone of the RV was improved with better contractility in group P compared to RV akinesia in group NP. Cardiac output (Figure 2A) was significantly better in group P ($1 \pm 0.2\,L{\cdot}min^{-1}$) than group NP ($0.7 \pm 0.2\,L{\cdot}min^{-1}$). Systemic blood pressure (Figure 2B) was lower in group P compared to group, but the difference was not significant, mean AP was: 75 ± 24 vs. 99 ± 15 mm Hg, respectively. RV coronary driving pressure (Figure 2C) was higher in group NP compared to group P (75.4 ± 6.6 vs. 59.4 ± 11 mm Hg) but the difference was not significant. In group P, RVP (Figure 3) dropped significantly from 29 ± 8 to 16 ± 6 mm Hg after 1 h of intermittent pulsation. In group NP, the mean RVP did not drop much after 1 h of intensive traditional therapy (from 30 ± 7 to 24 ± 2 mm Hg). PAP (Figure 4) also reduced significantly in group P, from 34 ± 5 to 22 ± 1 mm Hg; the group NP mean PAP was 36.6 ± 5.7 to 32.2 ± 5.07 mm Hg. Vascular resistance (Figure 5) decreased significantly ($p < 0.01$) in group P compared to group NP: PVRI dropped from 315 ± 39 to 174 ± 60 dyne·sec·cm^{-5}·kg^{-1} in group P, compared to 385 ± 114 to 352 ± 118 dyne·sec·cm^{-5}·kg^{-1} in group NP. SVRI dropped from 1144 ± 329 to 611 ± 70 dyne·sec·cm^{-5}·kg^{-1} in group P, compared to 1144 ± 329 to 1215 ± 315 dyne·sec·cm^{-5}·kg^{-1} in group NP. Pulmonary eNOS manifestation with the Western blot test (Figure 6) was not significantly different in pulmonary artery segments collected from group P compared to group NP, with actin optical density values of 0.90 ± 0.71 vs. 0.66 ± 52, respectively.

Discussion

This preliminary study has shown the efficiency of the pulsatile suit concept for the treatment of acute RV failure. The significant improvement in hemodynamics in group P compared to group NP revealed several positive points that might clarify the controversies regarding current RV failure management, as discussed below.

Regarding endogenous vs. exogenous NO, evidence of pulmonary and systemic vasodilatation in group P may be explained by the release of a potent vasodilator such as eNOS.[11] This presumed eNOS secretion could be induced by shear stress-mediated endothelial function enhancement following trouser pulsations on the congested hepatic venous capacitance.[12] Previous reports showed that oral administrations of exogenous NO donors, such as phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), were effective for management of pulmonary arterial hypertension in both animal models and clinical trials.[13–15] Tadalafil was applied based in its effect of potent pulmonary vasodilatation in the therapy of acute RV failure.[16,17] In our study, pharmacological agents failed to decrease the pulmonary afterload or improve hemodynamics in the non-pulsatile group; whereas the advantage of pulsatile therapy in terms of the exogenous NO donor was obvious in this study, although the exact mechanism of the presumed eNOS pathway is still unclear. This hypothesis of eNOS secretion from the hepatic endothelium could be refuted by the short biological half-life of NO.[18] Possibly, an undiscovered endothelial mediator(s) and/or mechanism(s) might have been triggered by this method. We observed similar results in other studies and models using different pulsatile devices (mask, tube, and catheter).

Interestingly, hemodynamic improvement and animal survival with complete recovery of the RV dyskinetic zone contractility in the group P did not correlate with the transmural RV coronary flow improvement, which was better in group NP. The increased RV coronary driving pressure, which was not significantly different in group NP, did not prevent hemodynamic deterioration in that group compared to group P. In other terms, RV contractility in group NP did not improve despite the maintained autoregulation of the coronary vascular bed.[19] On the other hand, the subendocardial resistance vessels are more sensitive to mediators of vasodilatation and endothelium-dependent dilators.[20] The important role of the RV subendocardial capillaries and myocardial microcirculation in hemodynamic improvement, rather than increased transmural coronary flow, has been demonstrated.[21] We also noted an impressive improvement in the microcirculation in preclinical tests on healthy human volunteers, using the trousers and a pulsatile mask (designed to improve cerebral circulation).

Table 1. Hemodynamic results of acute right ventricular failure therapies (pulsatile trouser vs. traditional)

	T1		T2		T3	
Groups	P	NP	P	NP	P	NP
Weight (kg)*	$10.8 \pm 1^{\dagger}$	10 ± 1				
Heart rate (beats·min^{-1})*	$87 \pm 10^{\dagger}$	95 ± 16	$104 \pm 27^{\dagger}$	107 ± 16	$92 \pm 12^{\dagger}$	89 ± 17
MAP (mm Hg)*	$79 \pm 11^{\dagger}$	81 ± 9	$91 \pm 33^{\dagger}$	93 ± 10	$75 \pm 24^{\dagger}$	99 ± 15
PAP (mm Hg)*	$20 \pm 5^{\dagger}$	17.2 ± 3.63	$34 \pm 5^{\dagger}$	36.6 ± 5.7	$22 \pm 1^{\S}$	31 ± 2
MRVP (mm Hg)*	$19 \pm 12^{\dagger}$	21 ± 3	$29 \pm 8^{\dagger}$	30 ± 7	$16 \pm 6^{\S}$	24 ± 2
LAP (mm Hg)*	$4 \pm 2^{\dagger}$	3 ± 1.3	$5 \pm 3^{\dagger}$	4 ± 1.3	$2 \pm 1.4^{\S}$	4 ± 1.7
RAP (mm Hg)*	$2.2 \pm 1.3^{\dagger}$	2.9 ± 1.3	$5 \pm 3^{\dagger}$	5.4 ± 1.52	$2 \pm 1^{\dagger}$	2.54 ± 0.76
Cardiac output (L·min^{-1})*	$0.8 \pm 0.3^{\dagger}$	0.9 ± 0.1	$0.7 \pm 0.2^{\dagger}$	0.7 ± 0.2	$1 \pm 0.2^{\S}$	0.7 ± 0.2
SVRI (dyne·sec·cm^{-5}·kg^{-1})‡	$817 \pm 367^{\dagger}$	812 ± 246	$949 \pm 522^{\dagger}$	$1{,}144 \pm 329$	$611 \pm 70^{\S}$	$1{,}215 \pm 315$
PVRI (dyne·sec·cm^{-5}·kg^{-1})‡	$168 \pm 61^{\dagger}$	182 ± 54	$315.2 \pm 39^{\dagger}$	385 ± 114	$174 \pm 60^{\S}$	352 ± 118

*Measured variables. $^{\dagger}p > 0.05$ between the P and NP groups. ‡Calculated variables. $^{\S}p < 0.05$ between the P and NP groups. LAP = left atrial pressure, MAP = mean arterial pressure, MPAP = mean pulmonary arterial pressure, MRVP = mean right ventricular pressure, NP = non-pulsatile group, P = pulsatile trouser treatment group, PVRI = pulmonary vascular resistance index, RAP = right atrial pressure, SVRI = systemic vascular resistance index, T1 = baseline, T2 = nearly 1 h after pulmonary valve disruption, T3 = 1 h after treatment.

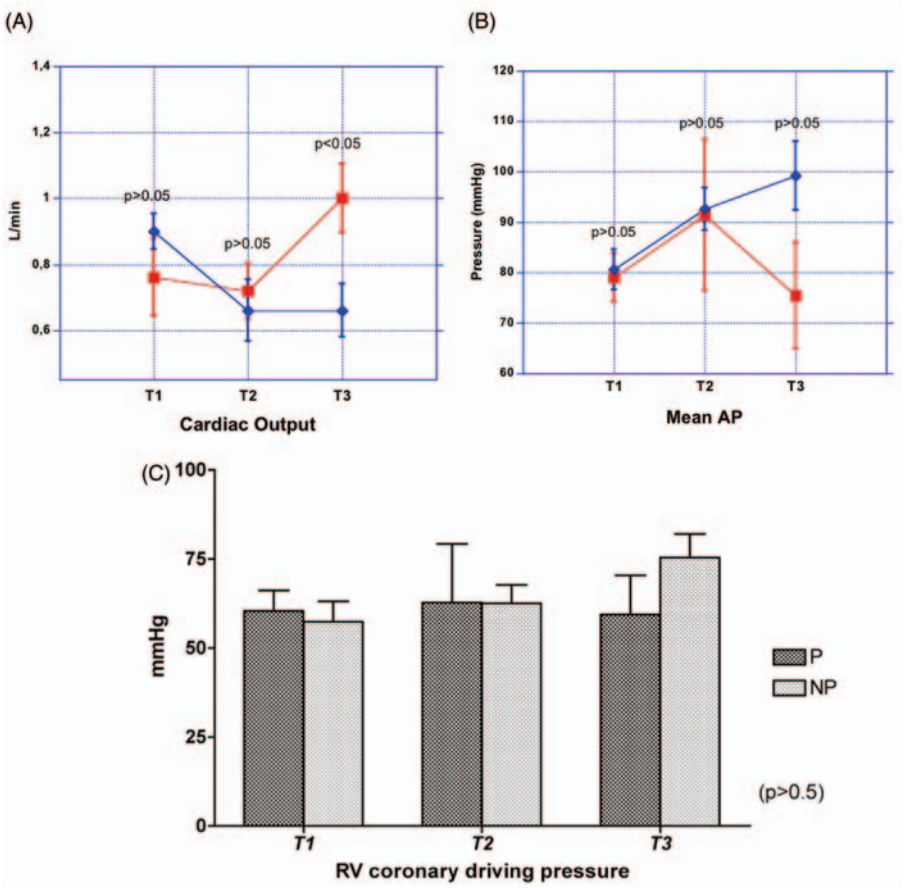

Figure 2. Microcirculation vs. coronary flow. (A) Cardiac output. (B) Mean systemic arterial blood pressure (AP) in the pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at 3 predetermined times: T1 = baseline; T2 after 1 h of shunt, and T3 = after 1 h of therapy. AP was non-significantly ($p > 0.05$) lower at T3 in group P compared to group NP. (C) RV coronary driving pressure showing a non-significant increase in coronary flow in group NP at the end of experiment.

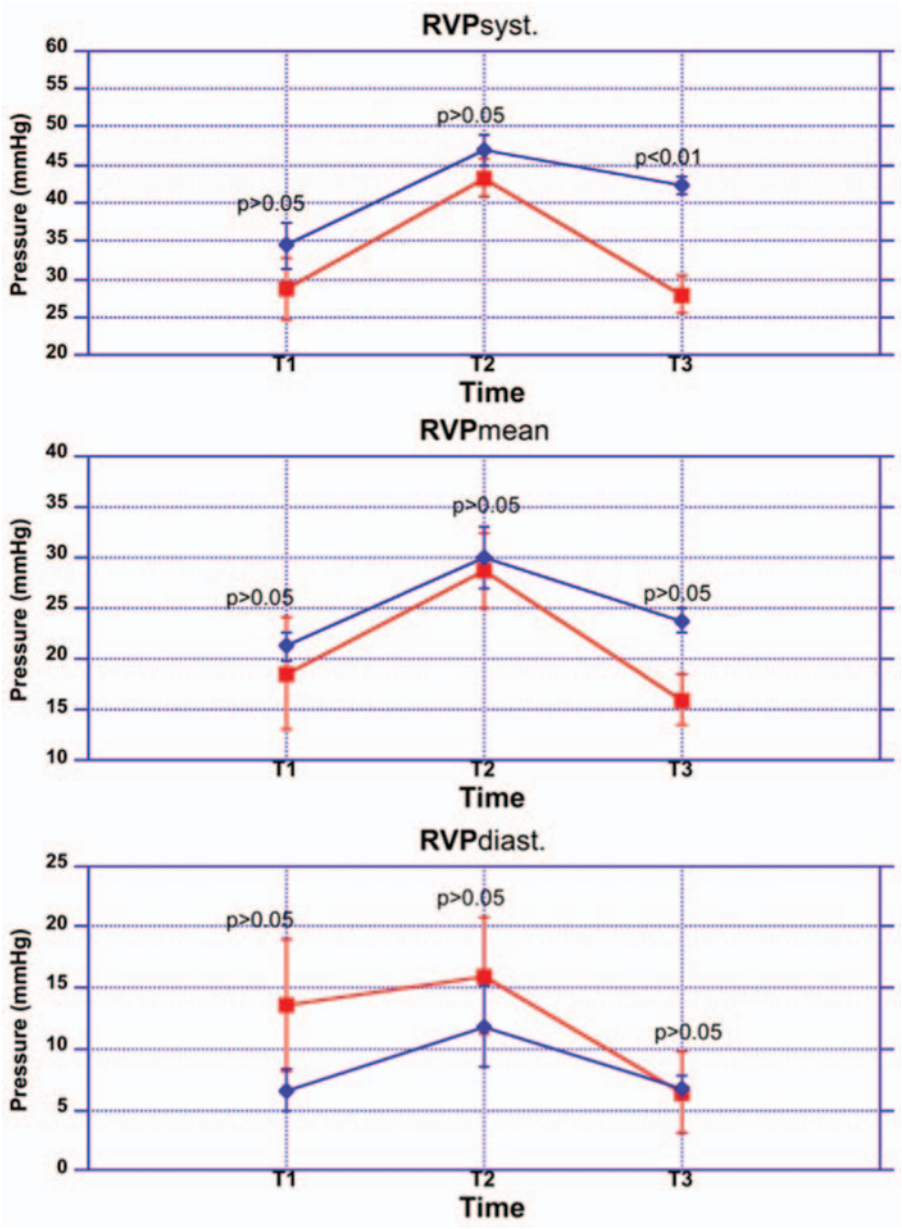

Figure 3. Right ventricular pressure: right ventricular pressure (RVP) in the pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at 3 predetermined times: T1 = baseline; T2 after nearly 1 h of shunt, and T3 = after 1 h of therapy. RVPsyst. = systolic RV pressure (upper panel); RVPm = mean RV pressure (middle panel); RVPdiast = diastolic RV pressure (lower panel). RVP was significantly ($p < 0.05$) lower at T3 in group P compared to group NP.

In this study, we created an acute pediatric model of RV failure (10-kg piglets). The induced RV failure was severe and rapidly fatal without mechanical assistance. Our experimental model was designed according to the prerequisites of clinical application in acute RV failure. Current models of RV failure (e.g. acute tricuspid regurgitation) usually overload compliant zones such as the systemic veins, before affecting the main RV pump;[22] this model using pulmonary valve disruption immediately overloaded the RV contractile zone with acute mechanical failure. The model also simulated postoperative hemodynamic dysfunction due to acute RV failure, such as in transannular RV-PA tract repair.[23]

The pulsations delivered were mainly focalized at the stagnant hepatic-splanchnic venous capacitance of the treated piglets. The device did not discharge the RV, conversely, it increased preload and decreased pulmonary afterload. To avoid incidents of obstructive venous return, the pulsatile impacts were delivered very gently and not synchronized with the cardiac diastolic phase. In one experiment in which the device was

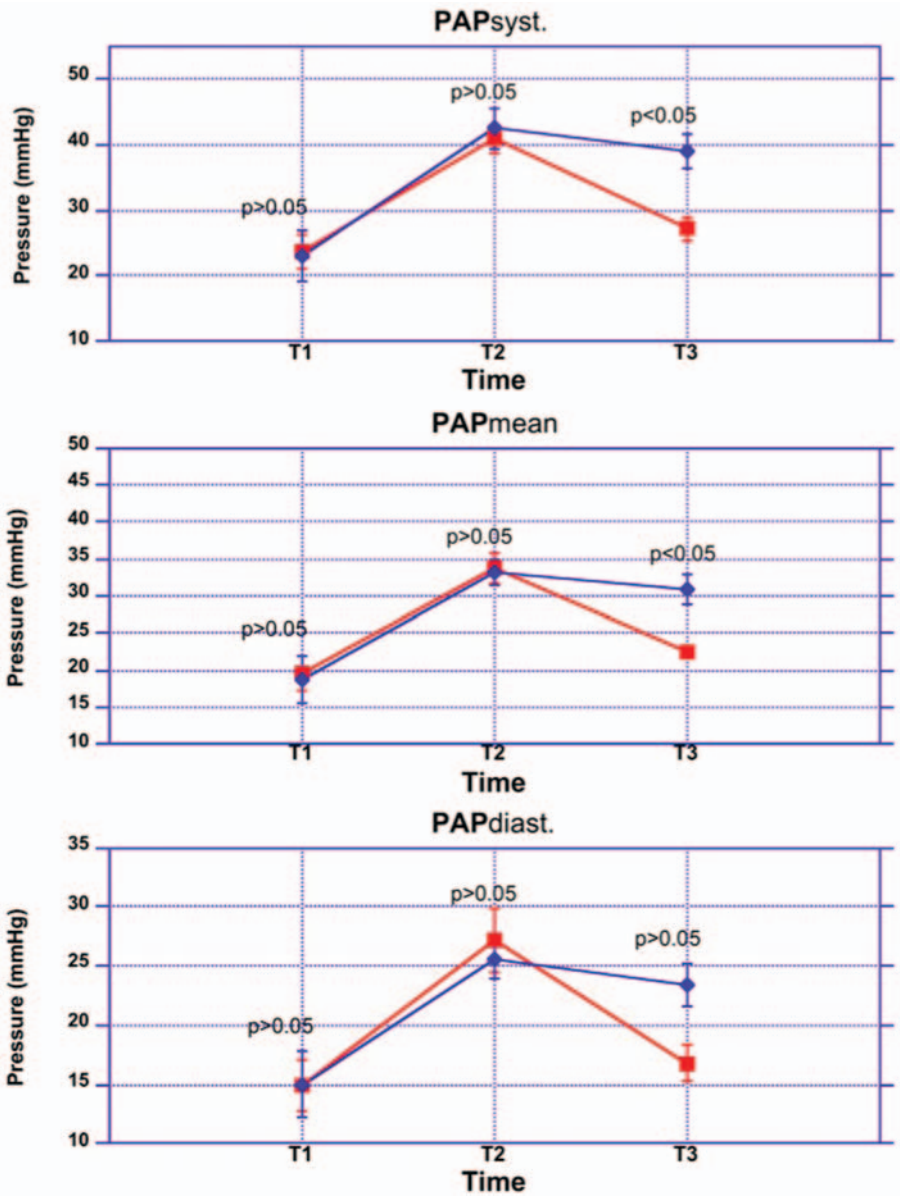

Figure 4. Pulmonary arterial pressure: pulmonary arterial pressure (PAP) in the pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at 3 predetermined times: T1 = baseline; T2 after 1 h of shunt, and T3 = after 1 h of therapy. PAPsyst. = systolic pulmonary pressure (upper panel); PAPm = mean pulmonary pressure (middle panel); PAPdiast = diastolic pulmonary pressure (lower panel). PAP (mm Hg) was significantly ($p < 0.05$) lower at T3 in group P compared to group NP.

synchronized with the diastolic phase with a low inflation pressure, the animal expired after a rapid rise of RA pressure (>16 mm Hg). Although, venous return is directly influenced by the respiratory pump, in this study, we fixed the ventilator frequencies between 15 and 22 cycles per minute, regardless of device pulsations (40 per minute). According to several trials, it is quite risky to increase the ventilator frequencies with severe lung congestion. In addition, trouser pulsations in low frequencies (<30 per minute) were less effective for hemodynamic improvement. Instead, the ventilator intensity was moderately reduced during device pulsations, according to intraoperative observations and hemodynamics, particularly RA pressure and blood gases. According to the hemodynamic parameters of the right heart (Table 2), there was a positive and rapid response to trouser pulsations rather than the medical RV failure therapy. In addition, the Western blot eNOS expression in pulmonary artery segments, which was not significantly different between groups, increased in group P despite the trouser pulsations. We observed this hypersensitivity of the right heart endothelium to shear stress stimuli using intrapulmonary pulsatile catheter therapy in acute pulmonary

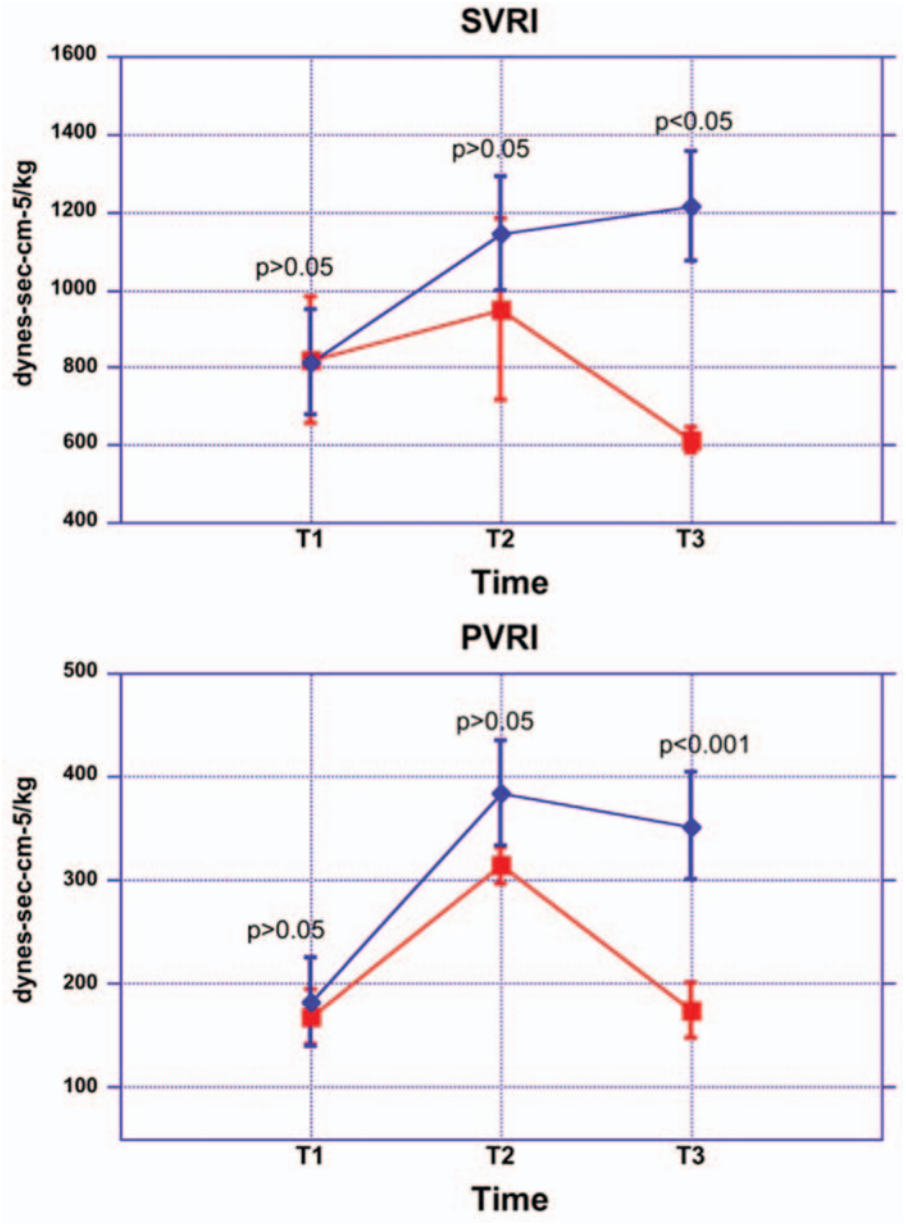

Figure 5. Systemic and pulmonary vascular resistances indexes: Upper panel: data of the systemic vascular resistances index (SVRI) in the pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at 3 predetermined times: T1 = baseline, T2 after 1 h of shunt, and T3 = after 1 h of therapy. Lower panel: pulmonary vascular resistances index (PVRI) in the pulsatile group (P; red color) and non-pulsatile group (NP; blue color).

arterial hypertension and acute myocardial ischemia in piglet models.

Cardiac assist-devices are frequently used for ventricular functional recovery or as a bridge to cardiac transplantation in severe congestive heart failure. At the same time, the morbidity and mortality of CAD are important, particularly in pediatric and RV failure patients.[24] In contrast, the pulsatile suit system provides circulatory support with an effective shear stress-mediated endothelial function. As a noninvasive device, it needs neither an oxygenator nor connecting cannulas. This minimizes the risks associated with current devices that must be primed and de-aired, in addition to hemolysis, vascular complications, and infections. The device is adapted to right heart biophysics and pathophysiology, allowing its application as an RV- or biventricular-assist device in association with a pulsatile tube device for a left ventricular-assist, which we are developing (patents: WO/2008/000110 & WO/2010/066899). The suit is not limited by size constraints

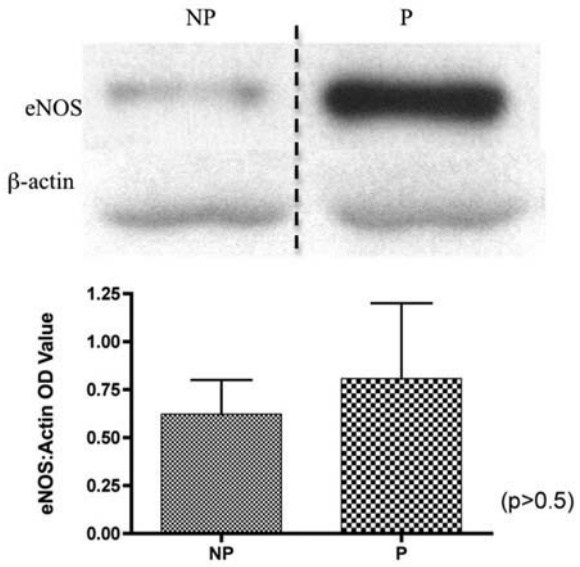

Figure 6. Pulmonary artery endogenous nitric oxide synthase (eNOS) expression with Western blot analysis. Upper and lower panels showing increased eNOS expression in pulmonary artery segments. NP = non-pulsatile group, OD = optical density, P = pulsatile group.

and pathological differences in heart failure. It is capable of supporting small neonates through to adolescents. The device is not synchronized to heartbeat in cases of heart failure, so it could be used safely in cardiac arrhythmia. Because of the simplicity of the circuit, setup can be performed within minutes in an emergency situation. Furthermore, the power console does not need high pressure so this could minimize its size and facilitate support of patients during transportation. These potential advantages also extend its application intraoperatively and in the early postoperative period.

Indications for the pulsatile suit can be defined according to 3 types of endothelial dysfunction pathogenesis: type A is endothelial dysfunction manifesting as heart failure, type B is endothelial dysfunction with normal heart function (e.g. diabetic, systemic arterial hypertension, idiopathic pulmonary hypertension, erectile dysfunction, cerebral ischemia), and type C is prophylactic in healthy individuals liable to - endothelial function pathogenesis (e.g. astronauts or the bedridden) as well as circulatory hemodynamic stimulus (e.g. athletics, anti-aging medicine). Contraindications are relatively few because it is a noninvasive device, but caution is advised in some cases such as hepatic cirrhosis, malignancy, open fractures, 3rd degree burns, biliary lithiasis, recent abdominal surgery, and colostomy. The inflation-deflation volume should be delivered at low pressure because patients with severely overloaded RV might not tolerate high-pressure impacts. This is functionally secured by the intermediate gelatinous layer of the suit, allowing homogenous propagation of the pulsatile impacts toward the inner elastic layer in low-pressure intensity. According to results of the study as well as ongoing clinical trials, it is recommended to have a pulsatile period of 20–30 min, which could be reviewed on the basis of hemodynamic data. Caution is also warranted because the exact mechanism of the endothelial vasodilator(s) mediators(s) is still unknown. For installation, a supine position is more convenient for bedridden categories. However, in certain circumstances (e.g. chronic heart failure patients) it is preferred to install it with the patient in a standing position, to amplify the enhancing effect of gravity as a factor of shear stress with more voluminous columns of venous capacitance. Whether the pulsations should be synchronized with the diastolic cardiac phase depends on the type of patient: in type A, the pulsations should be un-synchronized and kept below the heart rate (1/3–2/3 of heart rate) to prevent obstructive venous return accidents, particularly sudden of loading of RA pressure and respiratory distress; in type B, to restore endothelial function, it is recommended to synchronize the suit with the patient's diastolic phase. With type C patients, synchronization with the cardiac cycle is relative as the heart adapts hemodynamically according to its venous return (Frank-Starling Law).

This study described the use of the pulsatile suit system as an RV assist device in a pediatric model of acute RV failure. The device reduces and increases shear rate in the region of stagnant venous capacitance (zone 1). Thus it could be beneficial for RV bypass operations in infants because the device replaces the

Table 2. Hemodynamic parameters of the right heart circuit

	Group	PAP (mm Hg)*	RVP (mm Hg)*	PVRI (dyne·sec·cm^{-5}·kg^{-1})	CO (L·min^{-1})
T1	P	24 ± 3/15 ± 2	29 ± 4/14 ± 5	168 ± 27	0.8 ± 0.3
	NP	23 ± 4/15 ± 3	34 ± 3/7 ± 2	182 ± 42	0.9 ± 0.1
T2	P	41 ± 2/27 ± 3	43 ± 2/16 ± 5	314 ± 17	0.7 ± 0.2
	NP	42 ± 3/25 ± 2	46 ± 2/12 ± 3	385 ± 51	0.7 ± 0.2
T3	P	27 ± 2/17 ± 2	28 ± 2/6 ± 3	174 ± 27	1 ± 0.2
	NP	39 ± 3/23 ± 2	42 ± 1/7 ± 1	352 ± 52	0.7 ± 0.2

*Systolic and diastolic pressures. CO = cardiac output, NP = non-pulsatile group, P = pulsatile group, PAP = pulmonary artery pressure, PVRI = pulmonary vascular resistances index, RVP = right ventricular pressure, T1 = baseline, T2 = nearly 1 h after pulmonary valve disruption, T3 = 1 h after treatment.

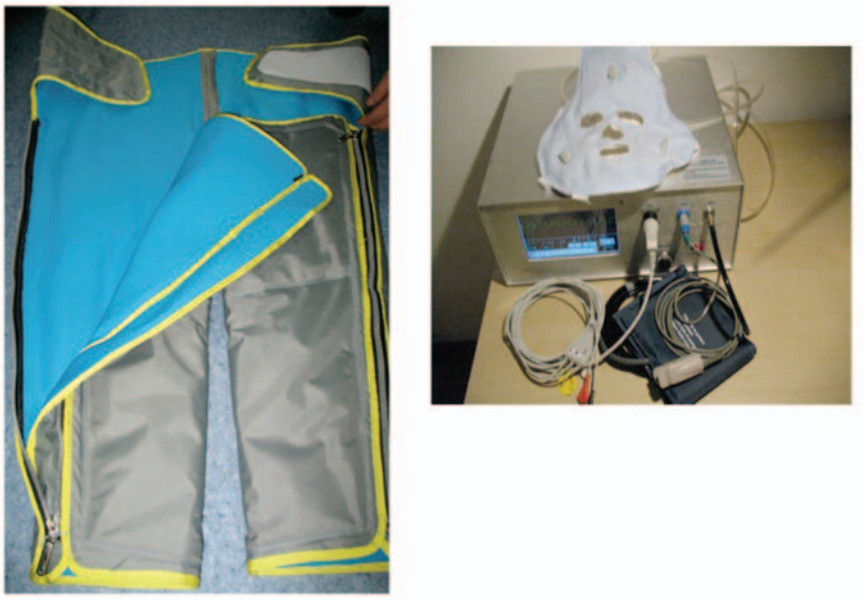

Figure 7. Pulsatile suit prototypes (human version). Left panel: pulsatile trousers. Right panel: pulsatile mask connected to a pneumatic generator and hemodynamic equipment (digital oximeter, electrocardiogram cable and sphygmomanometer cuff).

weakened respiratory pump in that very young age. Furthermore, by improving hemodynamics and RV contractility (zone 2), it may help in critical postoperative cases such as a first-stage Norwood operation. The suit increases RV preload and prevents the steal phenomenon at the septum (zone 3), which could help in patients with RV-dependent coronary circulation. This will increase the chances of a biventricular anatomical repair in most cases. Furthermore, it may be beneficial in acute-on-chronic RV failure that presents in adults with an old Fontan procedure or ischemic heart disease. In preclinical studies, the pulsatile trousers and mask prototypes were tested on healthy volunteers (Figure 7). There were significant improvements in hemodynamics and increased cerebral blood flow (measured with carotid Doppler echo) after 20 min of un-synchronized pulsations. Significant enhancement of the cutaneous microcirculation has also been observed, measured with a laser flowmeter (PeriFlux System 5000; Perimed) in an area remote from the pulsed zone (e.g., tip of the nose in mask trials, and fingertip with trousers).

The limitations include the fact that this study represents an acute hemodynamic shock model to assess the feasibility and reliability of the pulsatile suit therapy, evaluated in an emergency situation, according to hemodynamic data. The long-term effects of this device remain to be evaluated, and further investigations are underway in our laboratories. However, we concluded that the pulsatile suit concept could be used safely and effectively as an RV assist device in acute RV failure situations. These results may open a new era in the therapeutic approach for acute RV failure.

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Conflicts of interest statement

None declared.

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Chapitre X

Publications: Concept global

Nour S Flow and rate: concept and clinical applications of a new hemodynamic theory. In: Misra AN (ed) Biophysics. Intech, Rijeka, 2012, pp 17–76.

2

"Flow and Rate": Concept and Clinical Applications of a New Hemodynamic Theory

Sayed Nour
Therapeutic Innovations University of Paris XI, France

". . . From the heart arise the vessels which go to the whole body . . . if the physician lay the hands or his fingers to the head, to the back of the head, to the hands, to the place of the stomach, to the arms or to the feet, then he examines the heart, because all his limbs possess its vessels, that is: the heart speaks out of the vessels of every limb . . . If the heart trembles, has little power and sinks, the disease is advancing."
The Papyrus Ebers, c. 1534 BC (Stern,1875).

1. Introduction

Cardiovascular disease (CVD) is the first cause of mortality in developed countries, responsible for one death every 34 seconds and the estimated global annual cost is $ 403.1 billion according to recent statistics from the United States (Thom et al., 2006).

Furthermore, congestive heart failure (CHF) has been defined by the NIH, as the new epidemic in the USA, affecting more than 5 million new cases per year with a 5-year survival rate of less than 50% (Zickmund, et al. 2006).

Current therapies for CHF patients include medicinal provision of drugs such as cardiac glycosides, diuretics, AC inhibitors, anticoagulant (Couzens, 2009). However, medicinal therapies are usually insufficient necessitating complementary supports e.g., mechanically with cardiac assist devices (CAD) and/ or biologically with surgical procedures up till orthotopic heart transplants as an ultimate procedure.

Meanwhile, orthotopic heart transplant is still restricted due to the shortage of donors, plus operative morbidity and mortality (Schmauss & Weis, 2008).

Mechanical cardiac assist device (CAD) is usually used temporarily until the patient's hemodynamics improve, may offer an intermediate solution for the lake of donors as a bridge to a heart transplant (Park, et al., 2003), but in the heavy price of several disadvantages.

Permanent replacement of the heart with an artificial heart option is still a work in progress (Carpentier, 2011), with current technology having a short life expectancy. Thus, the artificial heart is primarily used as a bridge to transplant for patients wit biventricular failure. Furthermore the large size of an artificial heart limits its applications in specific categories, regarding body surface area (1.9±0.22 m^2), sex (95% men) and age (practically 0% children) (Roussel, et al., 2009).

Unfortunately, those aforementioned therapies still represent cost-effectiveness dilemma for health care systems in modern societies due to high cost, morbidity and mortality.

As a potential solution we are proposing a new therapeutic approach based on a fundamental revision of the entire circulatory system in correspondence to the physiopathology and physics laws applications with new generation of CAD.

The aim is directed to support and restore organ function, rather than to be replaced. Thus, it seeks to remedy the drawbacks of the state of present therapies and includes the innovation of new devices for providing cardiopulmonary and circulatory assistance.

This proposed therapy is based on a main concept (Think endothelial) and on a new hemodynamic theory entitled (Flow and Rate) that seeks to improve hemodynamics, organs microcirculations, restore and preserve the endothelial function by maintaining shear stress-mediated endothelial function with circulatory dynamics forces e.g., pressurized flow and shear rate (Nour, 2006).

1.1 Concept

Conceptually, the cardiovascular system is a closed pressurized hydraulic circuit (Figure 1), which is lined internally with endothelial cells (Samet & Lelkes, 1999; Furchgott, 1981).

Endothelium is constantly exposed to blood components and pulse pressure known as the tangential forces of shear stress (Hoeks et al., 1995).

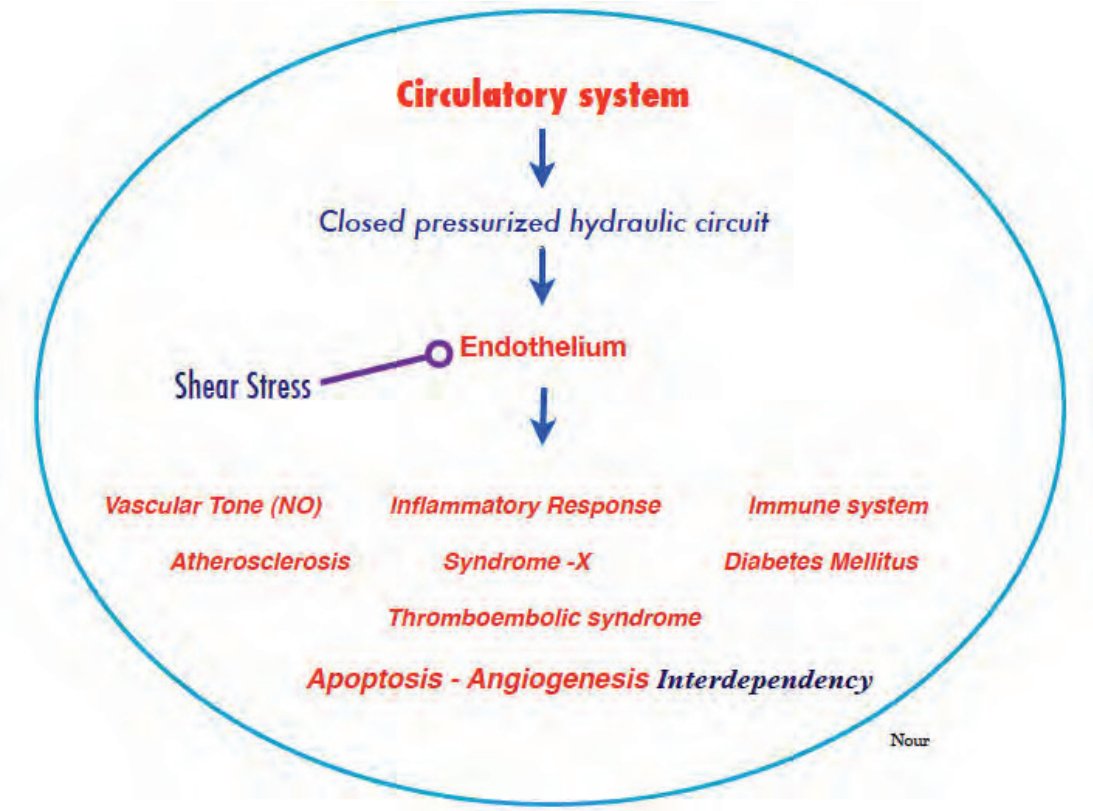


Fig. 1. Circulatory system's shear stress-mediated endothelial function

Shear stress controls and maintains endothelial function, which comprises the vascular tone by the synthesis of nitric oxide (NOS), blood coagulation, the inflammatory response, atherosclerosis, angiogenesis and apoptosis (Petrovic, et al., 2000; Limaye & Vadas, 2007; Lam et al., 2006).

In other terms, shear stress-mediated endothelial function controls embryogenesis, morphogenesis, organogenesis and maintenance of a healthy organism (Adamo, 2009).

In general, fluid movement in hydraulic circuits, which means momentum transfers with frictional losses, depends on driving forces, resistances, viscosity and conduits geometries (Kessler & Greenkorn, 1999).

The heart and peristaltic arteries represent the main circulatory driving forces that usually affect the left heart side.

Otherwise, accessory forces such as the respiratory pump, muscle pump, gravity, atmospheric pressure, oncotic pressure, skin baroreceptors, venous valves, pericardium, etc., are necessary to move up the steady blood flow at the right heart side (Nour, et al., 2009).

Endothelium controls vasoconstriction (e.g. catecholamine), vasodilatation with mediators like nitric oxide (NO) and vascular conditions with several processes like atherosclerosis and angiogenesis-apoptosis interdependency. This simply means that vascular resistances depend on vascular tone and vessels elasticity that are controlled mainly by shear stress-mediated endothelial function.

2. Fluid mechanics and cardiovascular pathophysiology

The clinical application of endothelial shear stress (ESS) should be realized in correspondence to cardiovascular biophysics, pathophysiological conditions as well as laws of fluid mechanics. This means a CAD should adapt the different criteria of each circuit of the right and left heart side (Figure 2), as follows:

1. The left heart circuit: it is characterized anatomically, by two high remodeling zones that represent the main circulatory pumps: the left ventricle (LV) and the aorta with the Valsalva as been shown on (Table1) and (Figure 2). Flow dynamics inside the Valsalva sinuses determines coronary ostia morphogenesis (Hutchins, 1988) and may contribute to a severe hemodynamic deterioration (Palmieri, 2001). So a shear stress-mediated endothelial function must be induced at the left heart side according to the Newton's principles by maintaining a physiological arterial pulse pressure (Feynman, et al., 2005). The LV almost, triples its myocardial mass during the first postnatal month with an important arterial angiogenesis. (Kozák-Bárány, 2001). According to Laplace's law, this LV remodeling could be enhanced by the posterior location of the LV (behind the RV), less limited by the pericardium and sternum, which increases the gravity effect, particularly in the neonatal supine position. The LV remodeling will be continued and maintained later on, influenced by ESS, the spherical shape of the LV (Yacoub, 1995), the elevated vascular resistances and the gravity effect at the aortic root. Disturbed flow dynamics at the left heart side induce atherosclerotic lesion (Samady, et al. 2011)), which is uncommon at the right heart side pulmonary arterial walls, most probably due to the constant delivery of ESS by the respiratory pump.

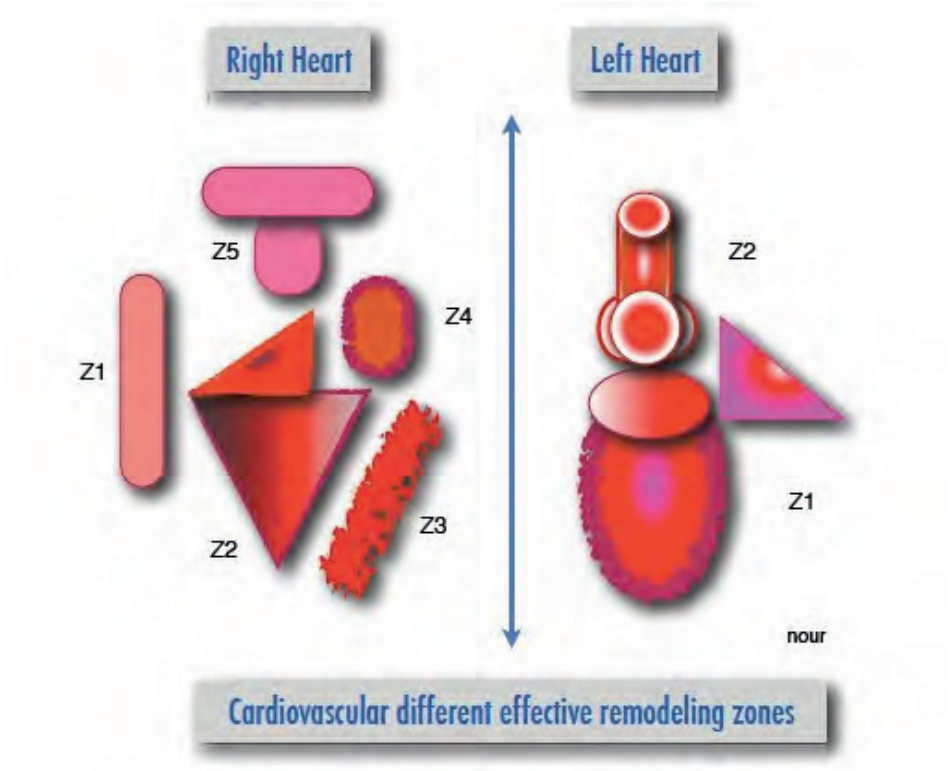


Fig. 2. Left and right heart circuits different remodeling zones

Zones	Sites	Remodeling	Main Factors
Z1	LV	High	↑ Laplace → posterior to RV less restricted by the pericardium; ↑ Newton → spherical shape (Tumkosit M 2007); ↑ resistances.
Z2	Aorta + Valsalva	High	↑ Shear stress (Newton): peristaltic pump + ↑gravity effect at the Valsalva; ↑ Laplace (less restricted external sheath at the arch), ↑ resistances.

Table 1. Left heart postnatal remodeling zones LV= left ventricle.

2. The right heart circuit: contrarily to the left, the right heart could adjust blood volume and shear rates at 5 different anatomical zones according to its physiological demands. In antenatal period, the right heart receives and pumps in equal rates more volume than the left, but keeps low remodeling due to pressure release through physiological shunts (Clark, 1987). After birth and shunts closure, both right and left ventricles share equal volume and rate inducing equal pulmonary and systemic cardiac output (CO), but remodeling remains inferior at the right heart side most probably due to venous steady flow and ventricular wall trabeculae. As shown in (Table 2) and (Figure 2), it could be identified by five different remodeling zones (Nour, 2009). Normally, the respiratory pump increases shear rates at the pulmonary endothelium externally creating an indirect or reversed pulse pressure shear stress (Newton). But with zones of steady flow and others with low pulse pressure the situation becomes more complex with physics

laws applications. In fact, both Bernoulli (Calvert, 2000), and Newton in addition to the gravity effect of Pascal's law as well (Humbert, 1947), must be considered to deliver a shear stress-mediated endothelial function.

Most importantly, the delivery of ESS with a CAD should be induced without disturbing the physiological remodeling of the right heart circuit (Buckberg, 2006). Direct induction of shear stress according to Newton's law like with an intravenous or intrapulmonary pulsatile perfusion must be avoided as it could induce serious hemodynamic conditions such as an irreversible pulmonary remodeling such us the Eisenmenger syndrome (D'Alto M, et al., 2007) or coronary bypass venous grafts disease. Also, the RV is preload dependant, that could not tolerate to be unloaded (Nour, 2009). This may explain failure of current pulsatile CAD in case of RV failure.

Zones	Anatomical site	Remodeling	Main Factors
Z1	SVC, IVC	Low	Absence of shear rates → Steady flow
Z2	A-V cavity	Mild	Trabeculae
Z3	Septum	Normal	Receiving interseptal left & right coronary supply
Z4	Infundibulum	High	↑ Coronary flow
Z5	PA tributary	Low	↓Pressure, Pulmonary Valve + Infudibulum

Table 2. Right heart postnatal remodeling zones (Nour et al 2009): SVC, IVC: superior & inferior vena cava respectively; A-V: atrioventricular; PA: pulmonary artery.

3. Hemorheological stock: the right heart circuit contains > 64% of blood volume surrounded by an important mass of endothelial cells. This natural stock of blood volume and endothelial mass can be stimulated by a proper pulsatile CAD, adaptable for right heart circuit's biophysics and physiopathology, for inducing shear stress-mediated endothelial function enhancement. Contrarily, to current evidence of high mortality of CHF patients associated with right heart failure (Haddad, 2011), the concept of the present therapeutic approach considers the right heart as a physiological backup for management of almost all types of hemodynamic and circulatory disorders, including CHF patients (Nour S, 2009). As been demonstrated on (Table 3), the right heart afterlaod could improve or deteriorates the global cardiac output (CO) and hemodynamic, for example nitrates therapies that could improve left ventricular MI by lowering the systemic afterload, may worsen and be fatal in case of RV ischemia (Haji, 2000).

Vascular Resistances	Status	Right heart	Left heart
Systemic	Low	Bad hemodynamic[1]	Good hemodynamic
Systemic	Elevated	Good hemodynamic[2]	Bad hemodynamic
Pulmonary	Low	Good hemodynamic	Good hemodynamic
Pulmonary	Elevated	Bad hemodynamic	Bad hemodynamic

Table 3. Dominancy of the right heart over the left heart through pulmonary vascular resistances (Nour, 2008):1= i.e. nitrates therapy in right ventricular ischemia; 2= i.e. epinephrine therapy with cyanotic spells

4. Pulmonary afterload: the influence of the right heart on hemodynamics is observed by the immediate postnatal drop of the pulmonary vascular resistances, triggered by the external shear stress-mediated endothelial function induced by the respiratory pump

(creating an indirect internal pulse pressure closer to Newton's law). Another example is observed in patients in squatting position during cyanotic spells of Tetralogy of Fallot (TOF) that increases the systemic vascular resistances (Senzaki, 2008) and increases the intrapulmonary flow and shear rates in a retrograde manner through the malaigned VSD to lower the pulmonary vascular resistances, followed by global hemodynamic improvement. The increased intrapulmonary shear rate that can be induced by adrenaline injection as well during the cyanotic TOF spells (Table 3), provides shear stress-mediated endothelial function approaching Bernoulli's law. Reduction of pulmonary vascular resistances is an immediate target for hemodynamic improvement that can be achieved by shear stress-mediated endothelial function enhancement directly with an intrapulmonary shear rate enhancement device (e.g. pulsatile catheter); or indirectly with an external pulsatile device (e.g. pulsatile suit).

5. Microcirculation: as is known, human being is a multicellular organism in which cellular biology performs a main role in terms of development, maintenance, proper operation and also failure of vital organs (Vincent, 2008). Maintaining good operation of organs by means of microcirculation in the organ constitutes a characteristic effect of the proposed concept. Microcirculations are controlled by plurality of endothelial mediators of vasodilators, which are dependent on shear stress (Koller, 1993) (Poelmann, 2008). Under normal hemorheological condition, microcirculation behavior approaches that of Newton's law. A symbolic example observed in athletics, high physical performance, which means shear stress-mediated endothelial function, could be achieved with slow heartbeat (shear rate) and increased stroke volume (pulse pressure). In contrast, in any abnormal hemorheological state, microcirculation presents behavior that approaches that of Bernoulli's law, as interpreted by the Fahraeus-Lindqvist effect in which plasma stuck at the inner vascular boundary layers while erythrocytes move faster at the center (Fahraeus & Lindqvist, 1931; Neri Serneri, 1981). This could explain absence of cyanosis in anemic patients with low hematocrite, unlike those patients with high hematocrite, as erythrocytes aggregations at microcirculations induce cyanosis with clinical signs finger clubbing (drumsticks fingers).

2.1 Cardiovascular pathogenesis

Endothelial dysfunction is responsible for almost all types of cardiovascular pathogenesis whatever congenital or acquired (Endemann et al., 2004)

The dependency of the endothelium on shear stress stimuli starts by the placental angiogenesis since the 6th gestational day, once there are normal hemorheolgical maternal factors (Heilmann, et al, 2005). Troubled shear stress forces due to an increased blood pressure (e.g.,preeclampsia) or low hematocrit (anticoagulant drugs), induces congenital anomalies and could interrupt the course of pregnancy (Aron, et al., 2003).

By the 8th gestational day of the intrauterine life, the embryonic vasculogenesis starts due to shear stress enhanced endothelial function, creating the first blood vessels followed by the appearance of the first fetal heartbeat by the 21st day (Meyers, 2007).

Furthermore, disturbed flow dynamics in the prenatal period, could induce congenital anomalies (Al-Ghazali, et al., 1989). Some symbolic examples of cardiac malformations are resumed on (Table 5) of cardiac malformations on (Table 4).

Flow disturbances	Congenital malformations
No flow → no grow	Hypoplastic left heart syndrome (Rao, 1994)
Homogenous flow	Heterotaxy syndrome (Prendiville, 2010).
Excessive flow	Agenesis pulmonary valves (Yeager, 2002).
Modified flow	Conotruncal defects: TGA, TOF, DORV, DOLV, (Rothenberg, 2003).

Table 4. Congenital malformations with troubled flow dynamics: TGA = transposition of great arteries; TOF= tetralogy of Fallot; DORV, DOLV= double outlet right or left ventricle respectively.

In the postnatal period, endothelial dysfunction is a major predisposing factor to hemodynamic troubles, circulatory disorders such as diabetes (Kapur A, De Palma R., 2007), arterial hypertension (Martini, et al., 2006), atherosclerosis (Chatzizisis, et al., 2007) and life-threatening conditions (e.g. cardiogenic shock, multiple organ failure). This could be induced by disturbed flow dynamics due to pump failure and/or elevated vascular resistances. As a symbolic example, right ventricular (RV) failure can occur either due to elevated pulmonary vascular resistances caused by pulmonary oligemia, pulmonary hyperemia; or due to RV pump failure caused by ischemia, congenital anomalies, arrhythmia, valvulopathy, and/or accessory circulatory driving forces failure like with failed Fontan's operation (Pereira & Shirali, 2005).

2.2 Types of endothelial dysfunction

Practically, and in a matter to facilitate the therapeutic approach for cardiovascular pathologies, endothelial dysfunctions could be classified into three categories as follows (Nour, 2009):

- **Type A**: endothelial dysfunction manifested with heart failure.
- **Type B**: includes endothelial dysfunction patients with endothelial dysfunction with normal heart function (e.g. diabetic, systemic arterial hypertension, PAH, erectile dysfunction, etc).
- **Type C**: represented by healthy individuals, liable for endothelial dysfunction pathogenesis under certain circumstances like disturbed atmospheric pressure and gravity (e.g. Astronauts, professional scuba divers, bedridden); fatigue, increased inflammatory responses, increased apopotosis (e.g. athletics, early aging processes).

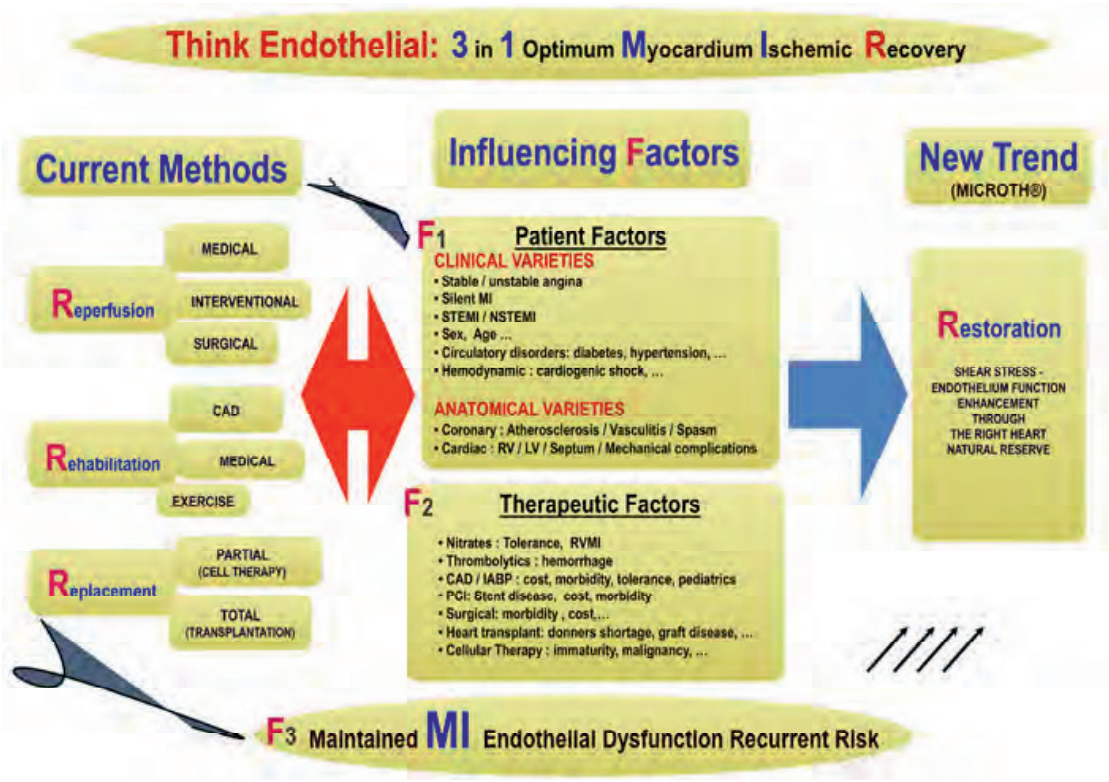
2.3 Endothelial dysfunction vs. current CVD therapies

Usually, endothelial dysfunction occurs as a consequence of pathological and/or interventional cardiovascular conditions, unfortunately with bad prognosis as there is no real curative option. A symbolic example, as been schematized in (Figure 3), regarding the current management of ischemic heart disease (IHD), which is still the leading cause of death so far. Except cracking or bypassing atheroma nothing has been done effectively until present.

As been resumed in (Figure 3): there are three symbolic "R" therapeutic options of myocardial ischemia which means: Reperfusion through an interventional and/or surgical approach; Rehabilitation, with physical exercise or CAD; Replacement with cellular therapy

(WU KH, et al., 2006) or heart transplants. Also there are three conflictual therapeutic factors "F": F1 due to patients clinical varieties like with unstable angina; silent ischemia; ST-elevated myocardial infarction (STEMI) or non-ST elevated myocardial infarction (NSTEMI); mechanical complications of IHD; cardiogenic shock (Berger PB, et al., 1999); age or sex. This is complicated by anatomical variation; variations in myocardial damage that affects the septum, right or left ventricular regions (Haji SA & Movahed, 2000); and variable coronary pathology, including normal, spasmodic, vasculitis, (Newburger, et al., 2004), or classical coronary atherosclerosis. Second factor (F2) is related to therapeutic defects like with nitrates tolerance (Abrams J, 1988); finally the most important factor (F3) is the maintained endothelial dysfunction (e.g. atheroma).

Unfortunately, all those therapeutic options could not resolve the problem, means to restore the main cause of dysfunctional endothelial atherosclerotic plaques (Davignon , et al., 2004). In addition, there are several varieties of MI due to other endothelial dysfunction pathogenesis rather than atherosclerosis such as coronary spasm (Kusama, et al., 2011) or congenital anomalies (McCrindle, et al. 2007), that could not be managed easily with angioplasty or coronary grafts (Gershlick & Thomas, 2007).



Otherwise, restorations of the endothelial function could be provided by the present concept (3R-in-one).

Fig. 3. Current therapeutic options for Myocardial infarction (MI)

3. Current CADs and endothelial dysfunction

In case of disturbed hemodynamic with heart failure, additional circulatory driving forces might be needed such as: a) Bio-assists with surgical procedures like the aortomyoplasty (Bolotin, et al (2001), cardiomyoplasty (Chachques, et al.,2005), and heterotopic heart

transplants (Onuzo, et al., 2000); and/or b) mechanical assists devices: like the cardiopulmonary bypass (CPB), left ventricular assist device (LVAD) (Seyfarth, et al., 2008)or right ventricular assist device (RVAD), and the artificial heart (Unger, et al.,1988).

In general, the present arts of cardiac assists devices can be classified in two categories:

1. Devices that increase coronary blood flow during diastole, in order to improve the oxygenation and thus the performance of the myocardium. This category includes the intra-aortic balloon pump (IABP), (Burkhoff , et al., 2006) and the enhanced external counterpulsation pump (EECP), (Bonetti, et al. 2003). These devices must be synchronized with heartbeat and unsuitable in case of cardiac arrhythmia; and
2. Devices that unload and bypass the heart pump: either partially as achieved by left ventricular assist devices (LVAD), right ventricular assist devices (RVAD), and by extracorporeal membrane oxygenation (ECMO); or completely like with biventricular assist devices, extracorporeal circulation (CBP), hetertopic heart transplant. It should be emphasized that ECMO partially deviates some of the venous blood to an external membrane oxygenator. ECMO does not completely unload the right ventricle (RV) and that may explain its successful applications in pediatrics patients who are more frequently vulnerable to RV failure (Wilmot, et al. 2011).
   As a matter of fact, development of CAD remains controversial due to the induced momentum energy losses with the tasks of increased morbidity and mortality.

Most probably, CAD may aggravate hemodynamics, leading to multiple organ failure and death due to several factors that could be directly linked to devices themselves or indirectly due to patients' related factors as follows:

1. Devices related factors:
   a. *Concept and design*: a CAD is typically a lumped model constructed according to laws of physics for driving a Newtonian compressible fluid inside a closed pressurized hydraulic circuits (Roselli RJ & Brophy, 2003), implementing rigid tubes with fixed diameter. Meanwhile in practices a CAD is confronted with a non-Newtonian fluid (blood, running in flexible vessels with different geometries). This confrontation between two opposite pressurized hydraulic circuits (Figure 4) creates a vicious circle of momentum energy losses manifested clinically by increased vascular resistances with endothelial dysfunction (e.g. hemorrhage, thromboembolism, inflammatory response, apoptosis, etc.), up till multiple organ failure.
   b. *Driving forces' drawbacks*: more precisely, roller or centrifugal pumps are usually used to circulate and perfuse blood between the patient and the external circuit most commonly in a steady flow mode of perfusion (Gravlee, 2008). Unfortunately even with biocompatible, materials the effect of sucking and pumping a fragile fluid like blood mechanically with impellers, propellers, or pulsed reservoir, inside narrow rigid conduits create a zone of turbulence and vortices with important energy losses (Geankoplis, 2005). This improper simulation of a ventricular function with current CAD, as it is practically impossible to replace a type III passive pump like the heart, by type II, or I pump (Anderson,1999).
   c. *Installations systems*: usually conduits of tubes, and cannula, made of biocompatible materials (e.g. PVC®, Dacron®, PTFE®, etc.), are used for connection between patient and CAD. In addition, those conduits need to be securely stitched to

cardiovascular tissues, diverted under the skin (tunnelization) to allow proper chest closure, then to be de-aired and checked for leakage or gas emboli before finally connected to their corresponding CAD. Furthermore, the distance between a CAD and the patient' inlet/outlet sites gives rise to dead space, creating an additional momentum energy losses zone(please refer to Figure 8). Finally, the procedures for installing such conduits need to be carried out by experienced surgeons in specialized centers on patients who are fragile, and who have usually already been operated on several times in the past, increasing the risks of morbidity and mortality (e.g. hemorrhages, vascular complications, infections, multiple organ failure).

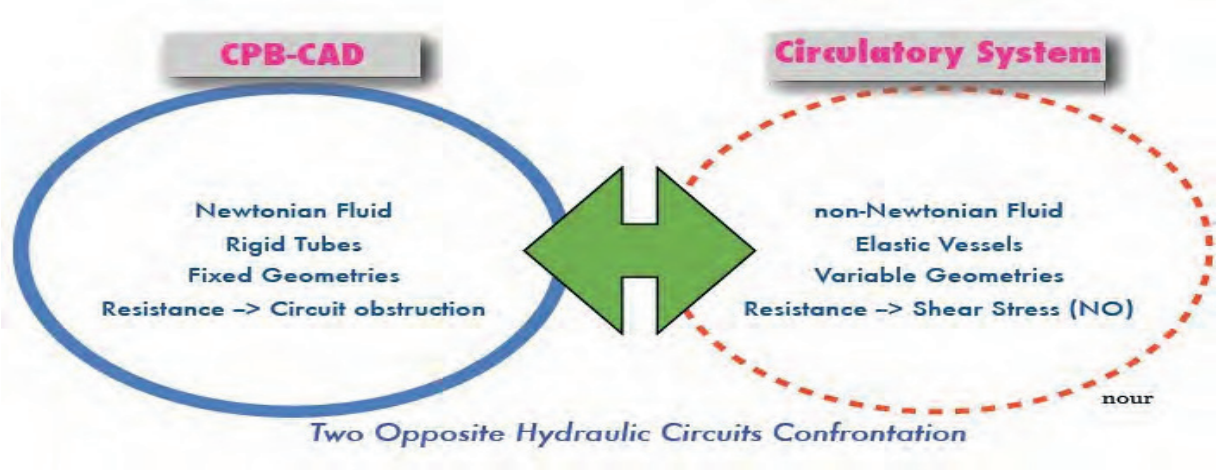


Fig. 4. Circulatory system and CAD create two opposite hydraulic circuits dilemma

2. Patients related factors: The aggravating factors inherent to the patients themselves can be of several kinds such as:
   a. Age, sex: most CAD devices are unsuitable for patients with small body surface area (e.g. children, female) since more than 80% of CAD devices are designed for body areas of more than 1.5 m^2, i.e. corresponding to adult heart patients. In addition CAD are generally first designed for management adult heart diseases and then miniaturized to cope with pediatric populations. However; pediatric patients are more vulnerable to hemodynamic disturbances caused by right heart failure due to congenital anomalies and they are vulnerable to vascular complications caused by small vessels geometries in content (Potapov, et al 2007). Adults usually suffer from ischemic left ventricular heart diseases with atherosclerotic vessels and they are therefore more vulnerable to vascular complications (Nour S, 2008).
   b. Etiology: fate of CHF patients with severe right ventricular (RV) failure (CVP>16mmHg) is worse, compared with those patients with left heart sided pathologies. Current therapies employing CAD to treat CHF patients with severe RV failure (Prutkin et al. 2008), still exhibit a high mortality rate (65%-95%), most probably due to insufficient understanding of the great difference between the right and left heart circuits (Sollano, 1998).
   c. Preclinical studies: in particular, the role of animal models in therapeutic evaluation, which is an extremely essential procedure before proceeding to clinical

applications of new CAD. However, there is still a gape between the chosen animal model and clinical realities as presented in the following examples:

i. Current models of myocardial infarction are unfortunately, driven by costs rather than clinical resemblance. For example, rat as a most popular selected model is far from human physiopathology with a heart rate> 400 bpm.
ii. Models of acute pulmonary hypertension (PAH), as often done either by hypoxia, monocrotaline, or systemic-pulmonary shunt. However, a lack of robust models of PAH, is still missing due to different spectra of lung tissue between species and humans (Robbins, 2004), (Bauer, et al. 2007).
iii. The biventricular heart failure models, often called for testing of cardiac assist devices, which remain difficult to achieve in animals. The most part of these mechanical assists devices are usually tested in computational version (Querzoli, 2011) or WindKessel models, away from the pathophysiological aspect in humans (Olufsen & Nadim A, 2004).

d. Miscellaneous: finally, the shortage of donors, immunosuppressive drugs drawbacks (e.g. malignancy); coronary atherosclerosis, follow up costs and surgical complications, all contribute to limiting the generalization of such treatments in practice.

4. Proposal

The present concept proposes clinical applications of these tangential forces of shear stress in order to regulate the endothelial function so as to improve the hemodynamic of patients, the overall microcirculation of vital organs, and, when it has failed, to reestablish normal operation of the cardiac pump in a manner that is as physiological as possible, without replacing any organs and without any traumatic intrusion, to provide a method that is as minimally invasive as possible.

Development of a CAD* with an optimum function, which means improving hemodynamics, increasing organ microcirculation, restoring and preserving deficient endothelial function in a diseased human being, should compromise the following steps: maintaining the circulatory flow dynamics in the patient's systemic and pulmonary circulations; and temporarily relieving the heart of its pumping function.

** CAD is referred to a "circulatory assist device", instead of the commonly applied term "cardiac assist device".*

More precisely there are three manners to stimulate the endothelium with a mechanical assist device as follows (Figure 5):

1. Direct internal endothelial stimulation that will be induced by an intravascular catheter device.
2. Indirect internal endothelial stimulations with a pulsatile perfusion flow generated by a pulsatile pipe (tube) device at the left heart side.
3. External stimulation (pulsatile suit) at the right heart side endothelial with gentle rhythmic squeezing of the venous and lymphatic capacitances reservoirs at the superficial veins and capillaries.

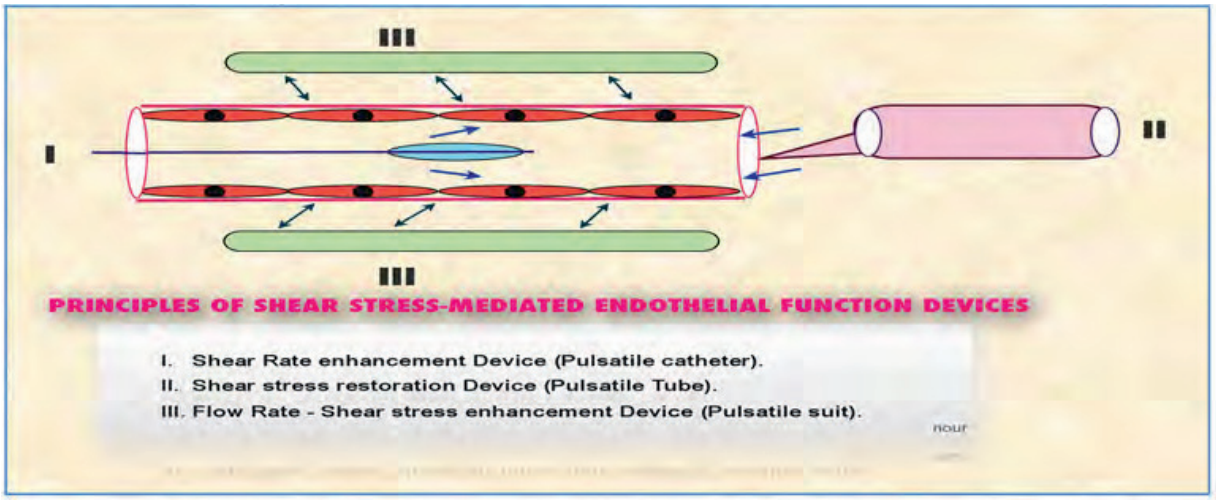


Fig. 5. Methods for shear stress-mediated endothelial function stimulations

According to the present concept, the method consists in using at least one device external to the patient's body and connected by at least a pipe and/or a specific connection element to:

1. Increase the preload of the right ventricle so as to improve myocardial oxygenation and so as to improve its contractility; and/or
2. Unload the left ventricle and diffuse regular pulsatile flow in the proximity of the aortic root so as to improve the hemodynamics of the left ventricle of the heart; and/or
3. Stimulate the endothelium mechanically by shear stress enhancement so as to release several mediators of endothelial vasodilators like nitric oxide (NO), to reduce the systemic and pulmonary vascular resistances (afterload).

5. Synchronization with the diastolic phase

The synchronization of these new pulsatile CAD with the heartbeat is strictly guided by the therapeutic indications according to types of endothelial dysfunction as follows (Nour S, 2009):

- Type A: this means in case of heart failure, CAD's synchronization is unnecessary and must be unsynchronized with heartbeat.
- Type B: synchronization of CAD with the heart is necessary to restore the endothelial function.
- Type C: synchronization of CAD is relative, because according to the Starling's law (Katz, 2002), the cardiac output (CO) adapts to the venous return (RV preload).

6. Devices

In known manner, the prior art constituted in particular by circulatory assistance systems such as LVAD, RVAD, Biventricular AD, etc., simulate the ventricular pump by complex driving forces.

In a manner that is very different, and indeed that is opposite in the physical sense of the word, the devices and methods of the present concept are designed to maintain circulation

in columns of blood within their own physiological containers as constituted by veins and arteries. The idea is to maintain a pulsatile blood stream complying with the biophysical and physiological standards of pulmonary and systemic circulations, by applying mechanical endothelial stimuli of shear stress.

One aspect of the devices and methods of the present concept enables shear stress endothelial stimuli to be increased, thereby enabling a microcirculation opening to be created in various organs of human body by means not only of conventional mediators of vasodilators such as nitric oxide, but also by means of other new vasodilators processing.

6.1 Pulsatile suit

In one aspect of the present method, blood is compressed from the outside of the body by means of a special suit referred to as a 'pulsatile suit", of the kind described in patents applications (WO/2008/000111) and (WO 2010/070018), which suit is used primarily to provide circulatory assistance to the right heart and secondarily as a device that makes it possible to obtain an overall hemodynamic improvement. The pulsatile suit is composed of three layers and must be suitable for the postoperative situations and provided with security features as following:

1. Inner layer made of elastic material (e.g. neoprene) to insure smooth tight massage like pulsed surge at the skin. 2. Middle sandwiched layer filled with gelatinous fluid, to alleviate the vigorous inflation/deflation, power induced by the driving force. 3. External layer made from tougher materials to keep the pulsed wave inwards toward the body. This part is equipped by security air releasing valve to prevent over inflation accident in case of mechanic defect. 4. Holes are previewed in the suit body, in order to facilitate medical administrations and prevent bedsores. 5. Layers thickness and design are modified according to age, body weight and indication of the patient. 6. The back portion of the trunk part of the suit (vest and belt) must not be inflatable in order to avoid any spinal, or back injuries. 7. Blood must be pulsed back from periphery towards the heart in a sloping progressive wave in longitudinal axis. Except at the chest part, pulsations must be started backward - forward towards the front, in a horizontal axis in such a manner to increase venous return within respect of the respiratory movement.

Naturally, this pulsatile suit has detachable parts and may take on various forms such as a hood, a pair of trousers, a jacket, a glove, a boot, or a sock. The parts could be reassembled together in one unit and wrapped tightly around the patient body through straps and zippers, as shown in (Figure 6) and as patents descriptions.

Figures 12 show such suit covering the bottom portion of the human body, which the therapist (doctor, nurse, or even the patient) can put into place without effort. The suit may be connected directly to an external pump, it may be actuated by the therapist himself or herself.

The structure serves advantageously to guide the pulsations it generates, progressively in the venous return direction. It thus constitutes a circulatory assistance device for the right ventricle (RVAD).

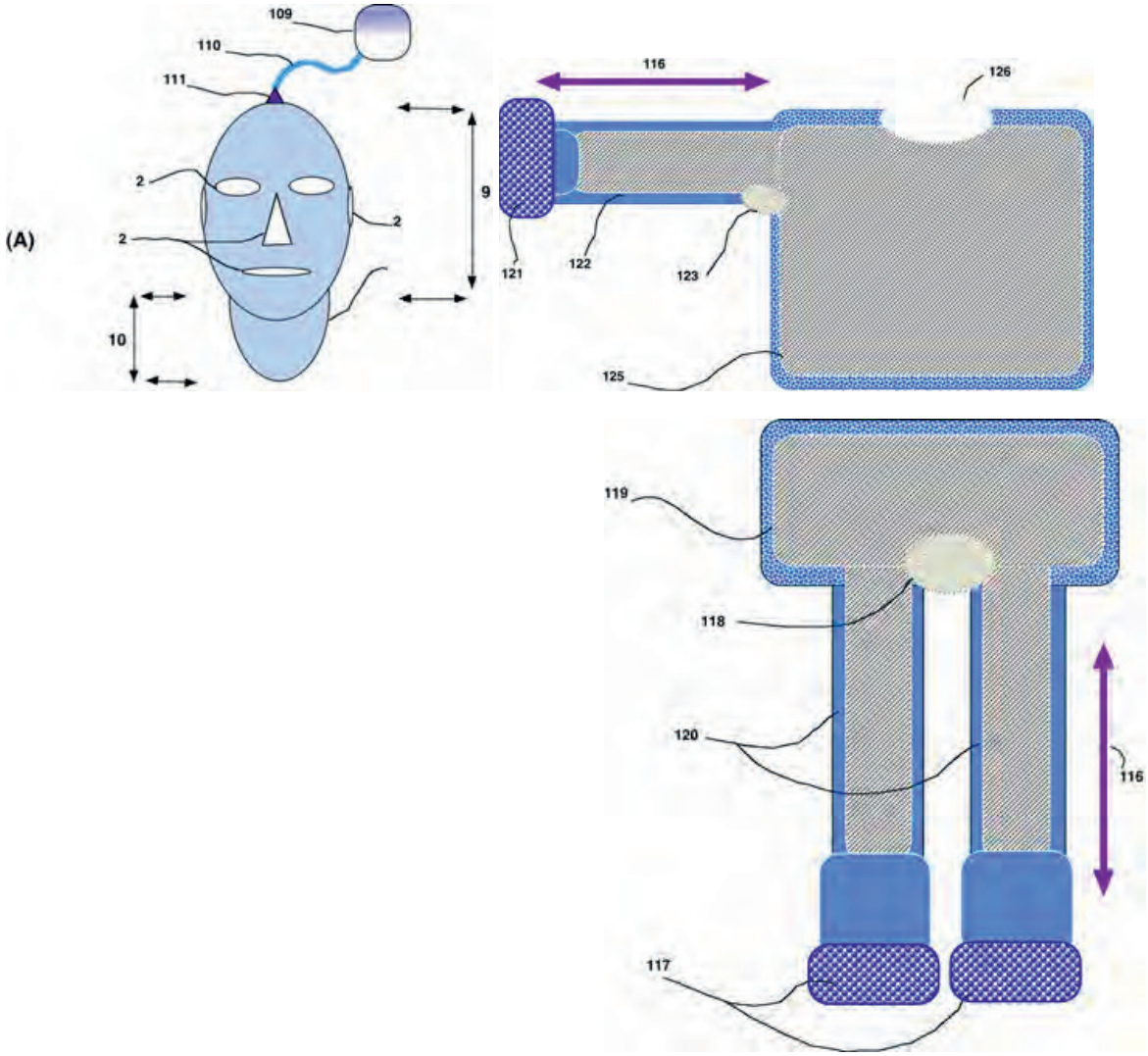
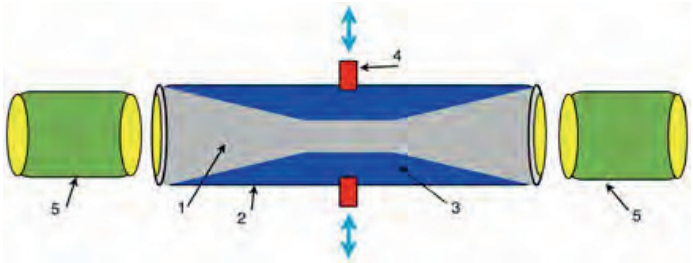


Fig. 6. Pulsatile suit CAD

6.2 Pulsatile tube

In another of its aspects shown in (Figure 7), the method implements at least one specific "pulsatile pipe" that serves to impart pulses to columns of blood, and that is preferably used in the context of providing circulatory assistance to the left ventricle (LVAD). Such a pipe is described in particular in patents applications (WO/2008/000110) and (WO 2010/066899). It may form part of a pulsatile medical kit that also includes a conventional pump (with or without oxygenator) placed at one end of the pipe, and an aortic cannula is placed by surgeon as close as possible to the patient's aorta. It is preferably prefilled in its intermediate space with an inert fluid such as helium, CO_2, etc. This diminishes the risk of embolism since the gas initially present in the pipe is discharged outside the circulation. In addition, the pressure forces required for operating the pulsatile device are reduced. It can readily be understood that this device is invasive to a very small extent. It generates pulsations in most effective manner and it is very easy to implement. It may be put into place surgically via a mini-incision or via a percutaneous approach and then synchronized with the patient's electrocardiogram.



1= Flexible inner tube; 2 = Rigid external tube; 3 = Intermediate chamber; 4 = Ports; 5 = Connectors

Fig. 7. Disposable pulsatile tube (pipe)

A disposable double lumens' tube, which is designed according to the principles of the "Bernoulli" 3rd equation: propagated pulsatile impacts transferred from the intermediate chamber (blue color), would move up the stagnant fluid boundaries' layers at the inner flexible tube (grey color), and push them towards the center in a mater to diminish the traumatic effects of blood and its components. Both tubes (inner & external) are sealed together at their extremities creating a sandwiched space between them with double central orifices connected to a pulsatile console. The tube is adaptable to a conventional CPB arterial line circuit through two standard connectors wedged at each end of the inner tube.

Practically, circulatory perfusing systems create a state of momentum energy losses that could be identified in 6 main zones (Z0-Z5) (Nour S 2008), as follows (Figure 8): (**Z0**) it represents the pre-oxygenator zone, where momentum energy losses depend on types of driving forces (e.g. (e.g. roller or centrifugal pump) to be deleted as well as the oxygenator, which is a major constant site of energy losses; (**Z1)** it is the zone downstream to the oxygenator, where energy losses depend on circuit conduit types (length, width, materials) and fluid viscosity; (**Z2)** it is represented by the pulsatile tube wedged at the arterial perfusion line between the oxygenator and aortic cannula; (**Z3)** it represents the pre-aortic cannula zone, which is the first effective pulsatile zone; (**Z4)** it represents the aortic cannula zone, where the effect of convergent (at the entrance) and divergent (at the tip) energy losses plays an important role (Cutlera D 1999); (**Z5)** it represents the perfused tissues started from the tip of the aortic cannula, causing important divergent momentum energy losses.

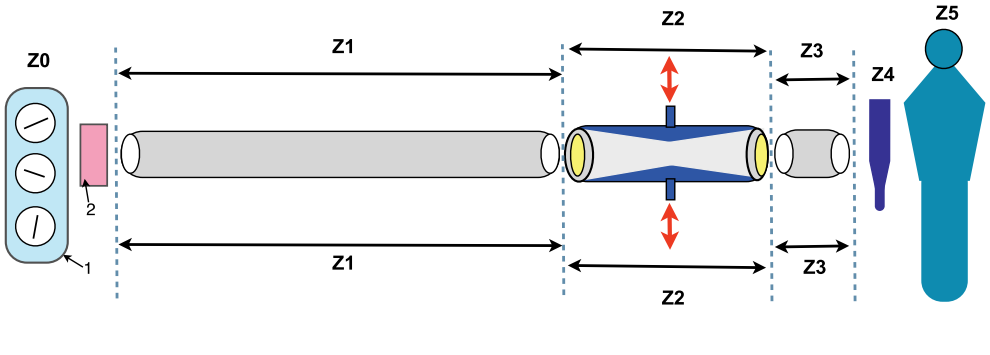


Fig. 8. Main momentum energy losses zone in a circulatory perfusion circuit

Accordingly, the pulsatile tube receives the steady flow from (Z1) downstream to the oxygenator, till (Z2) where the homogenous pulsations from the inner tube's walls move the stagnant laminar boundaries layers towards the center within total respect of Bernoulli's principle, with less vortices and better conservation of blood components.

At (Z3) where the effective pulsatile flow starts, theoretically this pre-aortic cannula zone represents a convergent diffuser with low momentum energy losses at the entrance of the aortic cannula. Meanwhile, a short (Z3)'s distance is requested to reduce turbulence and vortices that might occur due to strong-pulsed flow within a fixed geometries' tube. Furthermore, the pulsatile tube serves to reduce the empty space between monitor system and the tube itself, thereby giving rise to optimized operation with minimum pulsatile pressure; it is thus possible to envisage miniaturizing the device and correspondingly reducing the energy needed for its operation.

As seen in (Figure 12) a pulsatile pipe may be placed between the left subclavian artery and the right subclavian vein.

6.3 Pulsatile catheter

Another aspect of the present method comprises a "pulsatile catheter" comprising a conventional catheter that is surrounded by an inflatable element over a portion of its length (Figure 9). Such a catheter is disclosed in patent applications (US/2011/021987) and (WO 2009/136035).

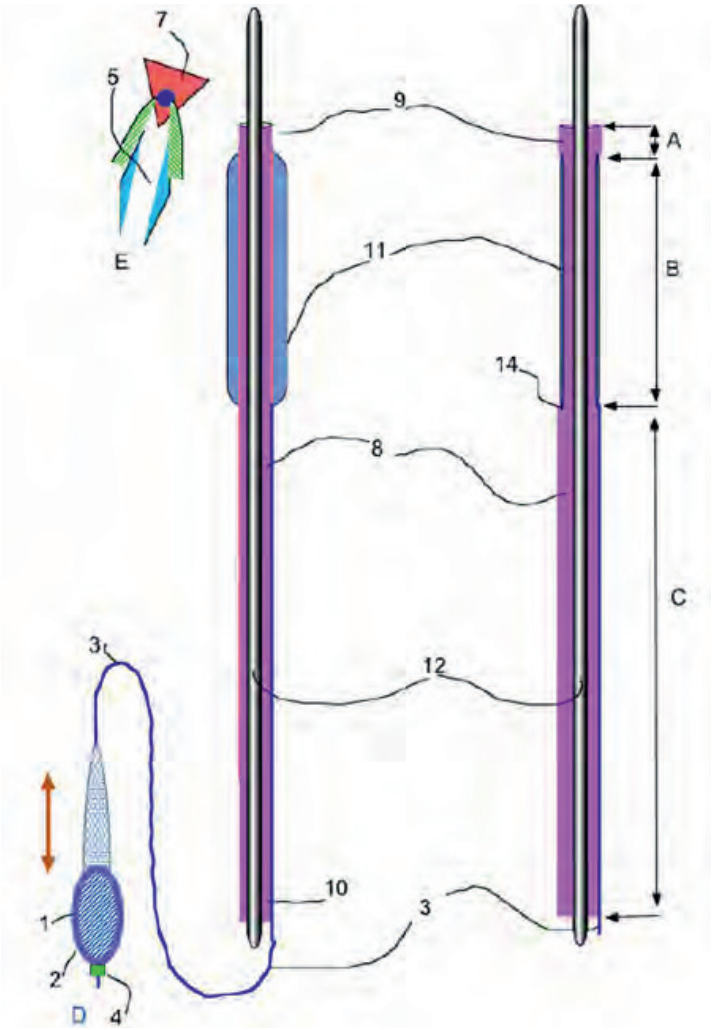


Fig. 9. Intravascular shear rate enhancement device

According to (Figure 9), the invention relates to a device for creating a pulsating inflation of an inflatable component (11) of a catheter (8), comprising: a bag (1) that can be filled with fluid (2); a bag compression means (5) capable of compressing said bag (1) in a pulsed manner; and a connection means (3) connecting said bag (1) to said inflatable component (11) of the catheter (8) and allowing the fluid (2) to move between said inflatable component (11) and said bag (1).

Advantageously, the inflatable element in place around the catheter presents in the deflated state an outside diameter that is less than that of the remainder of the catheter. Naturally, the inflatable element is connected to external inflation means suitable for generating pulsations during inflation. The device advantageously makes it possible to avoid excessively enlarging of the point where the catheter is inserted into a blood vessel.

Such a device is used in particular for PAH with increase in the afterload of the right ventricle (right ventricular failure); the catheter is placed in the trunk of the pulmonary artery by a percutaneous venous approach, preferably in association with a pulsatile suit.

6.4 Pulsatile console

An example of the pulsatile console (Figure 10), is described in patent application (US 2011166515) that console is very simple in design and easy to use. The console enables determined pulsatile pressure to be created and applied to a pipe, a catheter, or ay other equivalent means. A simple source of fluid under pressure such as a bottle of an inert fluid, or of liquid under high pressure constitutes the continuous source that is transformed into a pulsatile source by the pulsatile console as disclosed therein.

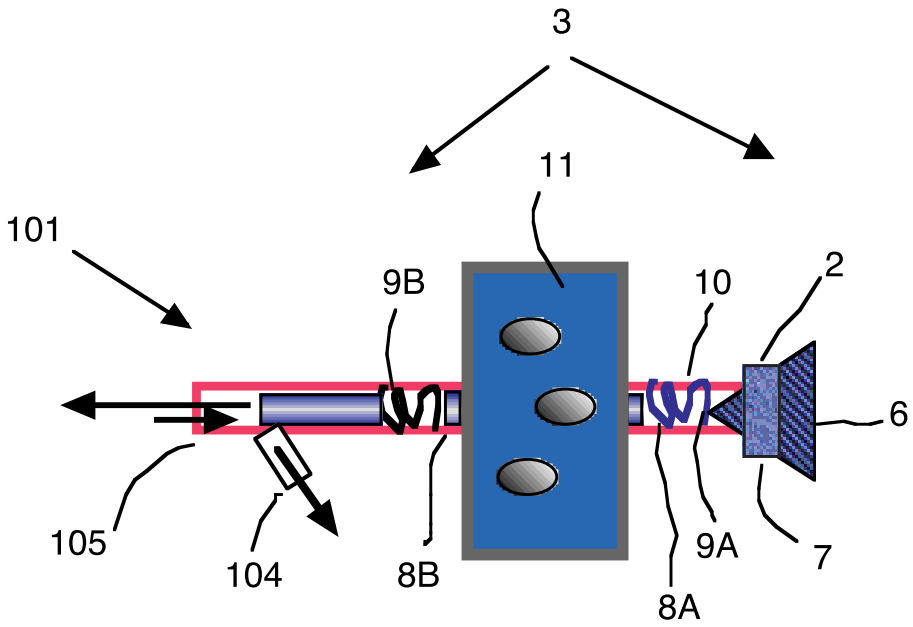


Fig. 10. Portable pulsatile console (Tu-Master).

The invention relates to equipment for applying a determined pulsatile pressure to a medical device, comprising: a withdrawing means (2) designed to withdraw fluid from a source of fluid in continuous flow at high pressure; a conversion means (3) designed to convert said fluid into a fluid in a pulsatile flow at low pressure; at least one application means (105) for applying said fluid, as a low-pressure pulsatile flow, to said medical device; and a means (104) for removing said fluid.

6.5 Smartcan

According to yet another aspect of the present method, a secure and almost non-invasive connection is provided between the patient and external mechanical systems for providing circulatory assistance (Figure 11). This aspect may be achieved by a device of the kind described in patent application (WO 2011/089162).

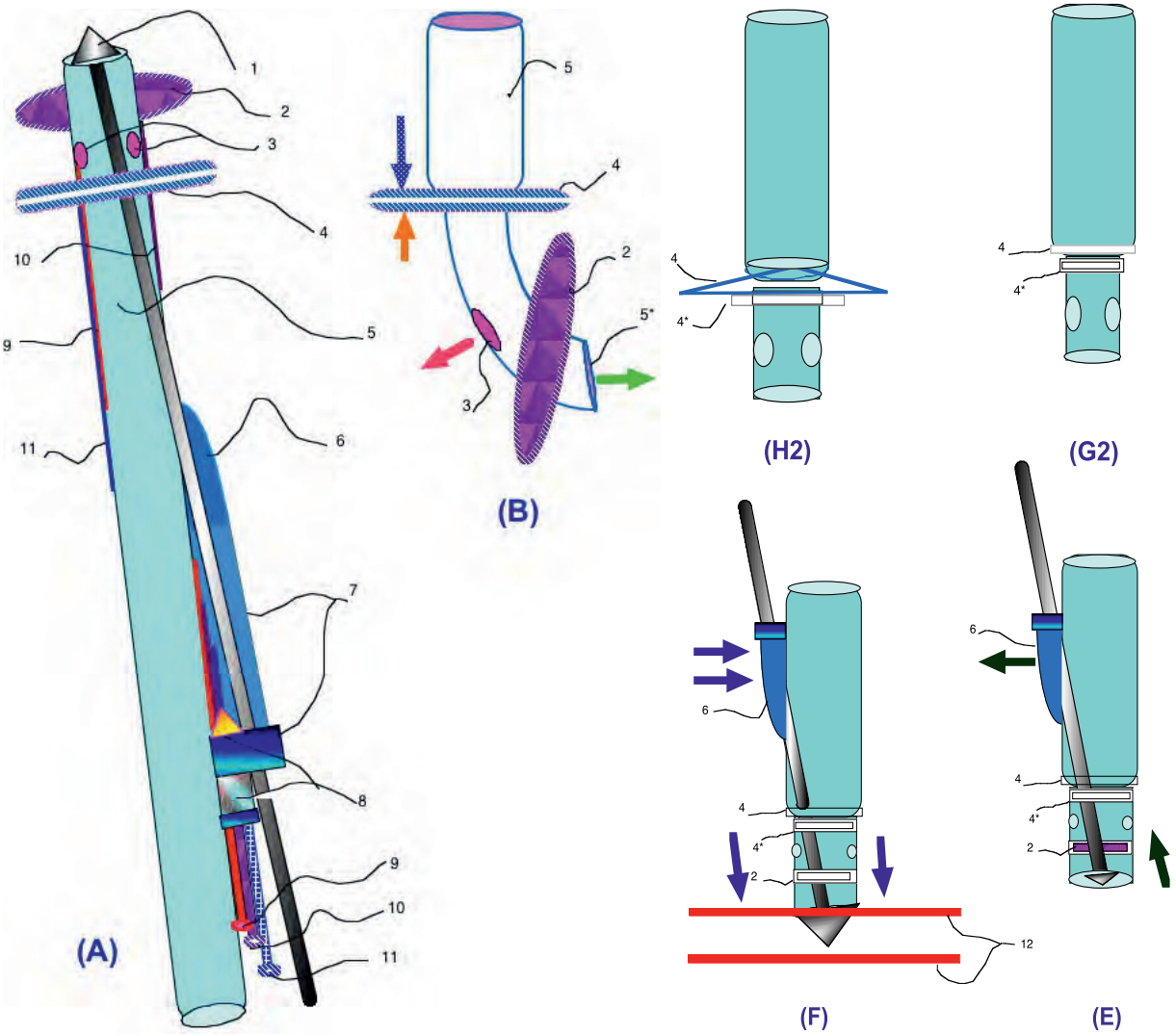


Fig. 11. The Smartcan conduit device

That device entitled the "Samartcan", makes it possible advantageously to group together all of the tools that make it possible to obtain a cardiovascular approach that is effective, fast, safe, and inexpensive. Thus, the tool enables a single operator, makes it possible to avoid all of the traditional steps such as incision, suture stitches, purse strings, etc. That simplifies the operation. Operating costs are thus significantly reduced.

Such a tool may be put into place and moved with assistance and remote guidance, e.g. echocardiography. This avoids blind guidance under the patient's skin for connecting the patient with an external circulatory assistance machine as with prior art methods. Such a connection gives rise to complications for the patient such as infections, hemorrhages, problems of closing the chest, etc.

In an advantageous manner, such a tool can be used as an aortic cannula, a cardiac cannula, a vascular catheter, or indeed as tubing for cavity drainage.

Such a tool, and more precisely the body of the device, is preferably prefilled with a liquid such as heparinized serum in order to reduce the risks of gaseous embolism and in order to shorten operating time.

In a novel and advantageous manner, the distance between such a tool and the patient is very small. In other words, the distance between a circulatory assistance machine (CAD) and the puncture sites (on the patient) is very short; in particular when implantation is performed close to the subclavian artery. This characteristic greatly reduces the energy losses that are inherent to existing devices.

The present invention relates to a single-use device to be used in surgery each time that a vascular approach by means of cannulation or catheterization is deemed indispensable (cardiopulmonary bypass, anesthesia, emergencies, resuscitation), particularly during cardiac surgery or interventional cardiology. Said novel device substantially includes a body (5), a sealing system consisting of two inflatable diskettes (4), a control connector for inflating and deflating the diskettes (4), a tubular unit (6) and a flexible guide (1). Upper right panel: shows a Smartcan with folded (G2) and unfolded (H2) external diskettes. Lower right panel: shows the Smartcan manually controlled guide wire before (E) and after penetrating a blood vessel (F). Left panel global schema of the Smartcan (A) and the proximal end (B) with the intraortic obstructive dikette (2), the cardioplegia delivery holes (3).

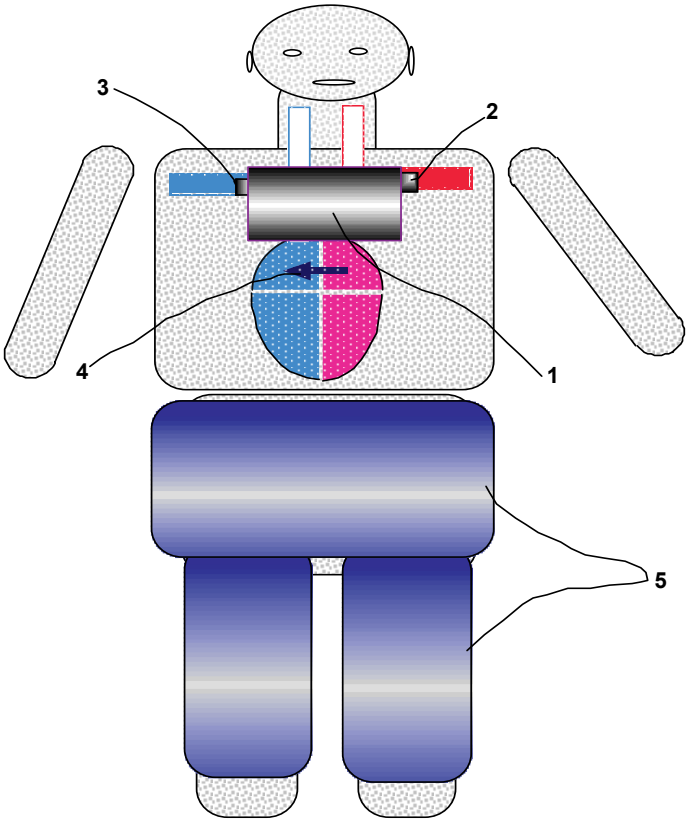
6.6 l'Orthèse cardiaque

According to another US patent application in pending, the various devices (pulsatile pipe, suit, and catheter, in particular) implemented in the present disclosure are synchronized together or separately as a function of the patient's hemodynamic parameters.

It relates to a novel therapeutic technique and method of providing mechanical circulatory assistance using a CAD that is minimally invasive. The CAD improves hemodynamics and microcirculation, and restores the endothelial function when it is insufficiently stimulated, particularly for a patient suffering from congestive heart failure (CHF).

The device complies with the patient's hemodynamic parameters as a function of breathing frequency and cardiac rhythm. Heart rhythm is detected by the electrocardiogram or by pacemaker as a function of variation in arterial pressure and/or in systemic and pulmonary resistances.

Synchronizing the pulsatile suit, thereby increasing venous return (preload) and reducing afterload, needs to be performed without hindering the frequency of breathing and without increasing central venous pressure above 16 mmHg. The pulsatile frequency of the suit may be less than the cardiac frequency of the patient (one-third to two thirds of the heartbeat).



Right panel: l'orthèse with complete suit (full throttle option); left panel: l'orhèse with bottom trouser; 1= pulsatile pipe set; 2 = left subclavian artery tip; 3 = right subclavian vein tip; 4 = arrow defines intraseptal drainage; 5 = pulsatile trouser set; 14 = vest; 15 = sleeves.

Fig. 12. l'Orthèse Cardiaque

In contrast, the pulsatile pipe associated with the patient's electrocardiogram may be synchronized with cardiac rhythm and the pulsatile catheter may be faster than heart rate.

In particular, the devices and methods of the present CAD avoids problem associated with blood circulation through two well-separated circuits (systemic and pulmonary) that are constituted by the vessels and arteries of the patient and by the mechanical circulatory assistance device (s).

All of those pulsatile means enable variations in blood pressure to be created in vessels in application of the physical laws that apply to non-Newtonian fluids. They allow stagnant blood to be moved in compliance with Bernoulli's law, i.e. from the walls towards the insides of the vessels. This therefore gives minimizes the traumatic effects on erythrocytes.

When the heart pump, and in particular the left ventricle, is to be relieved (unload), the practitioner will use a Smartcan device in a version that enables an incision via the tip of the left ventricle or a left intra-atrial transeptal incision.

Similarly, when regular pulsations are to be produced and diffused close to the aortic root, the same device may be inserted as an arterial perfusion cannula in the root of the aorta or in the subclavian artery via a percutaneous approach or by echocardiographic guidance.

Figure 12 shows a patient fitted with a pulsatile suit that covers the bottom portion of the body; in addition, a pulsatile jacket is placed around the patient's thorax and pulsatile sleeves are placed on each of the patient's upper limbs. In this embodiment of the invention a pulsatile pipe is placed between the subclavian artery and the subclavian vein.

Furthermore, the present CAD is suitable for managing various types of heart failure, regardless of the right or left etiology.

On the right heart, by putting pulsatile suit into place, the device makes it possible to reduce the stagnation of venous capacitances; by implementing a pulsatile catheter, it is possible to reduce the pulmonary afterload.

On the left heart putting a pulsatile pipe into place enables physiological pulse pressure to be maintained and directly serves to improve overall hemodynamics by reducing systemic vascular afterload.

Thus, the methods and devices according to the present disclosure may be defined as a circulatory orthosis, as opposed to prosthesis. Unlike orthotopic transplantation, the present disclosure makes it possible to keep the patient's heart in place, thus allowing the patient to wait in relative comfort for a histocompatible donor.

The present method provides bridging treatment prior to transplantation, thereby improving prognosis and morbidity by restoring patient's hemodynamics. As a reminder, present-day mortality is higher for right ventricular failure it lies in the range of 65% to 95%.

The present disclosure makes it possible to restore the endothelial function progressively by maintaining quasi-physiological shear forces on the endothelium; consequently, there is a significant improvement in the function of myocardium, thus making it possible avoid subsequent transplants.

The present disclosure provides and approach that is invasive to a very small extent, since it avoids risky surgical acts, in particular, the invention avoids sternotomy and/or thoracotomy which can be put off until subsequent transplantation.

The devices and method of the present disclosure thus makes it possible to cope with the shortage of donor and with the numerous problems that are associated with antirejection treatments.

In addition, the present CAD is adapted to all age categories, from newborns to patients of great age and/or patients that are most clinically fragile.

7. Experiments

These devices were evaluated in vitro, as well as with clinical volunteers. The in vivo study was approved by the Animal Research Facility at Sun Yat-Sen University and conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No.85-23, Revised in 1996). In original pediatric animal models of acute cardiogenic shock state, created in

piglets. We have avoided any premedication or any prophylactic medical support that may interfere with the endothelial function (e.g. atropine, β-blockers, etc.). Only mechanical cardiac support was provided with the evaluated device compared to traditional therapies in control groups. The clinical volunteers were medical doctors included the author.

7.1 Evaluation of the pulsatile tube device

Perfusions of the circulatory system with devices like the cardiopulmonary bypass (CPB) and CAD disturb endothelial shear stress (ESS), which is responsible for the post-cardiotomy syndrome, increasing liabilities of clot formation, bleeding, disseminated syndrome, etc (Bick et al., 1976)) (Abshire, 2009). This endothelial dysfunction syndrome is most probably occurred due to steady flow, foreign surfaces and the severe momentum energy losses. To overcome these side effects different therapeutic strategies are currently applied (Nour S, 2003), such as: *a) pharmacological supports* using antifibrinolytic (Cooper, 2006), inotropes, vasodilators, platelets, etc. (Nardell, 2009), but with some side effects as well (Ishida, zt al., 2004); b) *normothermia:* that becomes more practiced in CPB with some proven advantages over hypothermia (Pouard, et al., 2006), which may be explained because blood is nearly Newtonian at 37.2°C (Box, et al. 2005). Meanwhile, the benefits of normothermia on myocardial protection and microcirculation improvements remain controversial (Rastan, et al., 2008), as the myocardium is already protected with doses of cardioplegia, while the perfusion of microcirculation is more or less helped by the Fahraeus-Lindqvist effect due to hemodilution; c) *total or partial absenteeism* of CPB: that becomes popular with proven postoperative hemodynamic advantages, *but* it is still a challenging technique reserved for selected groups of patients (Shroyer, et al., 2009); d) *pulsatile perfusion flow devices:* in a matter to keep ESS some pulsatile CPB have proven advantages clinically and experimentally (Ündar, et al.,1999); (Undar, et al. 2006). Despite that, recent studies recommend the unphysiological steady flow (Voss, et al., 2010). This may be explained by pulsatile CPB inadequate curves with the necessity of a double perfusion pumps system to compensate the oxygenators momentum energy losses. Instead associating an intra-aortic balloon pump (IABP) with a conventional CPB, as a cost-effective manner (Onorati, et al., 2007), creates turbulent zones of vortices (Geankoplis, 2005), with vascular complications (Sanfelippo, et al.,1987) and controversial effectiveness (Kadoi Y & Saito, 2000).

Alternatively, the pulsatile tube represents a potential solution for those aforementioned CPB and CAD drawbacks

The pulsatile tube device (Figure 7), was evaluated as a potential solution for these CPB and CAD drawbacks. A device prototype was tested in vitro (a mock circuit) for energy losses studies and in vivo as a LVAD, also the tube prototype was associated in the in vivo study of a Bi-ventricular assist device (l'orthèse).

7.1.1 In vitro study

Materials and methods: a double lumen tube prototype as shown in (Figure 13), composed of: a) external polyvinyl chloride (PVC) (20 cm length, ½ inch diameter). b) Internal Polytetrafluoroethylene (PTFE) (18 cm length, 12mm diameter), reinforced with latex membrane (condom), as a protector against the PTFE micropore. c) 2 connectors (¼ inch) introduced at each end of inner tube and wedged to the PVC tube and securely sealed by

external adhesive straps and rings. A small animal ventilator (HX-300 TaiMeng Technologies Inc®), was applied as a pulsatile generator.

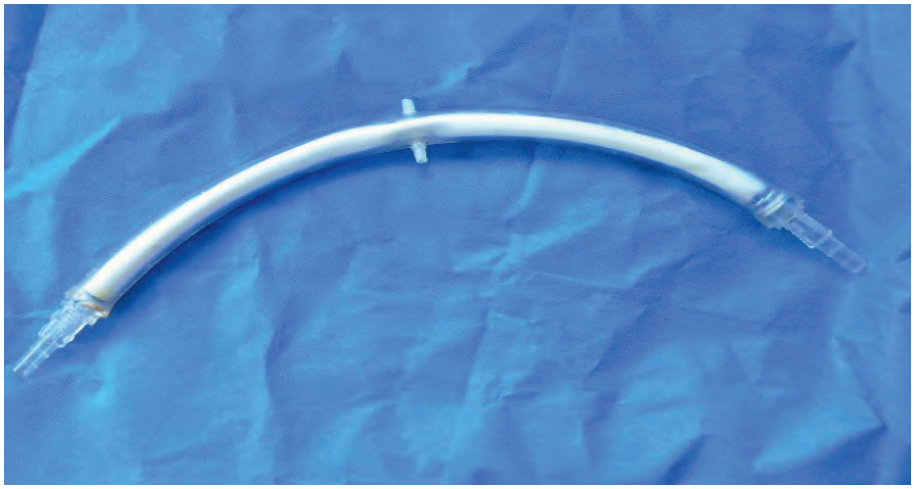
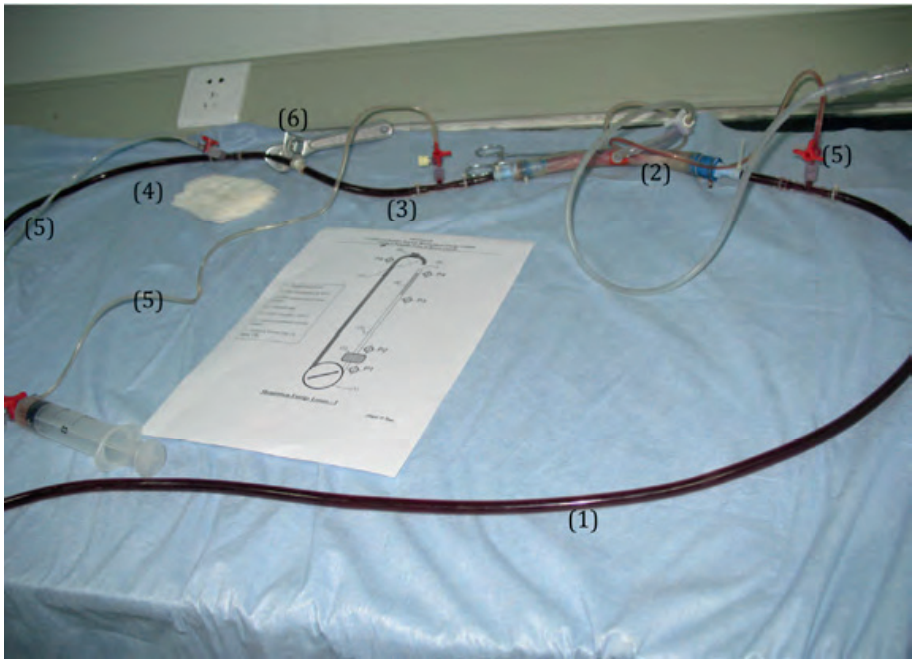


Fig. 13. Pulsatile tube prototype (Dr. Nour)

Mock circulation: with slight modifications from the literatures (Undar et al;, 2006), (Wang, et al., 2009), it was composed of (Figure 14): a roller head pump (Cobe® Cardiovascular Inc.), pediatric oxygenator (Sorin® Lilipput 2 Ecmo) and filter (Sorin® Group hemoconcentrators), primed with fresh piglet's blood mixed with dextrane in concentration of (2/3) and (1/3) respectively. A pediatric arterial line circuit, PVC tube (1.5 m length), 14 FR aortic cannula (DLP® Medtronic, Inc.), venous line (1.5 m length) and simulating vascular resistance partial clamp, positioned downstream to the aortic cannula.



1 = arterial perfusion line; 2 = pulsatile tube; 3 = aortic cannula; 4 = venous line; 5 = pressures lines; 6 = partial tube clamp (simulated resistance).

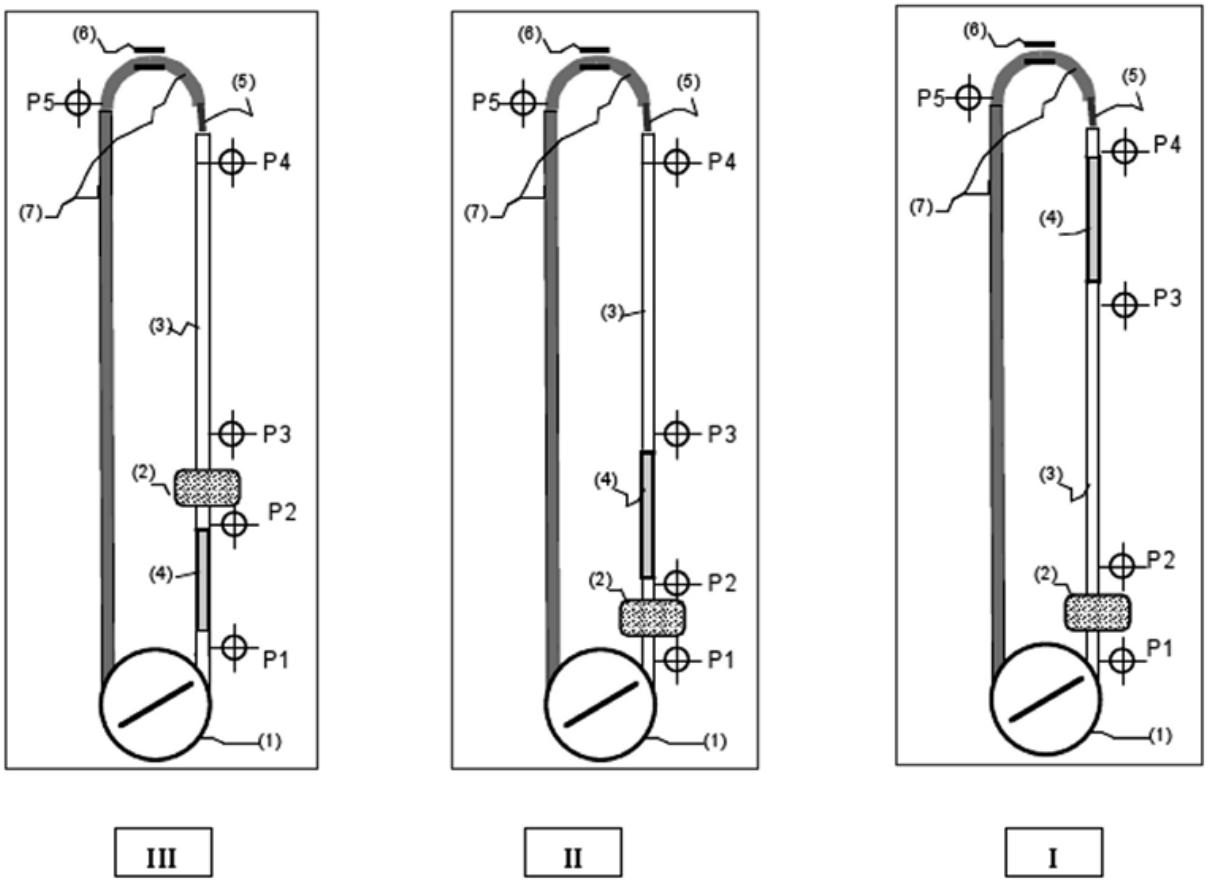
Fig. 14. Mock-circulation: energy losses circuit (I)

7.1.2 Methods

With variant pump flow rate (400, 600, 800 and1000 ml/min) and fixed pulsation rate (110 bpm), we have compared circuit momentum energy losses during steady and pulsatile flows in 3 different tube positions as following:

- Energy losses I: the tube was positioned downstream to the oxygenator at 6 cm from the aortic cannula (Figure 15-I).
- Energy losses II: the tube was positioned downstream to the oxygenator at 150 cm from the aortic cannula (Figure 15-II).
- Energy losses III: the tube was positioned between pump and oxygenator (Figure 15-III). This position conceptually simulates current devices of pulsatile CPB.

Recorded pressure curves: first in a steady mode, then pulsatile by switching the tube's generator on, were collected at 5 remote distances spots: up and downstream: to oxygenator (P1, P2); to tube (P3, P4) and to resistance (P5) which simulated a systemic arterial perfusion curve in patients.



{I} = Pulsatile tube was positioned at *6 cm* distance from aortic cannula; {II} = Pulsatile tube positioned at *150 cm* distance from aortic cannula; {III}. Pulsatile tube wedged between roller pump and oxygenator. 1 = roller pump; 2 = oxygenator; 3 = arterial line; 4 = pulsatile tube; 5 = aortic cannula; 6 = resistance (tube clamp); 7 = venous line. P1, P2, P3, P4, P5 = perfusion pressures recording spots.

Fig. 15. Mock-circulations with 3 different tube positions

7.1.3 Statistics

Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test hemodynamic data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

7.1.4 Results

As been resumed in (Table 5) and (Figures: 16 & 17), momentum energy losses were significantly increased with the pulsatile tube in positions: III and II, compared to position I. Furthermore, there were observations of an increased perfusion pressure at P5 from the initial P1 of those groups (II and III), signifying severe turbulence at the post-cannula zone, which theoretically, corresponds to patient's aorta. There were minimum momentum energy losses with the steady flow in position. I, In contrast to positions II and III, there were important vortices with obstructive zones that created a sort of retrograde flow even before pulsations.

	Groups	P1	P2	P3	P4	P5
	NP (I)	32,5 ±1,3	31,3 ± 1,3	30,3 ± 0,5	30,3 ± 0,5	30,8 ± 0,5
1 -	NP (II)	36,3 ±1,3	37,8 ± 1	39,5 ± 0,6	38,5 ± 0,6	39,3 ± 0,5
	NP (III)	40,3 ±1	42,3 ± 1	43 ± 0,00	42,3 ± 0,6	43 ± 0,00
	Pm. (I)	34,5 ± 1,7	34,5 ± 1,3	33,5 ± 1,7	32,3 ± 1	31,8 ± 1
2 -	Pm. (II)	39,3 ± 0,5	40 ± 0,8	40,8 ± 0,6	40,5 ± 0,6	40,3 ± 0,5
	Pm. (III)	43 ± 1,2	46 ± 2,2	46,3 ± 1,5	44 ± 0,8	44,8 ± 0,5
	Ps. (I)	72 ± 3,5	81 ± 11	92,8 ± 4,9	98 ± 11,5	92,8 ± 5,6
3 -	Ps.(II)	97,3 ± 7	92,3 ± 6	90 ± 11,2	81,3 ± 7,5	82,3 ± 8,4
	Ps. (III)	84,3 ± 6,6	79,8 ± 5,9	79,8 ± 5,5	69 ± 3,9	69 ± 4,2
	Pd. (I)	(-)4,4 ± 3,2	(-)6,5 ± 7,4	(-)13,6±11,7	(-)35,3±8	(-)33,5±13,3
4 -	Pd. (II)	(-)1,1 ± 6,2	(-)7,8 ± 4,4	(-)0,8±9,4	5,6 ±8,4	13 ±3,2
	Pd. (III)	0,5 ± 10	5,3 ± 5,3	7,5 ± 7,5	20,3 ± 3,8	20,3 ± 0,5
	PP (I)	76,4 ± 3,4	87,5 ± 11,8	106,4 ± 15,9	133,3 ± 17,7	126,3±18,6
5 -	PP (II)	98,3 ± 7,9	1OO ± 10,4	100,3 ± 10,3	75,7 ± 15,4	66 ± 6,1
	PP (III)	83,8 ± 9,2	74,5 ± 8,7	72,3 ± 12,6	48,8 ± 7,1	48,8 ± 4,7

P = pressures in (mmHg); I,II,III: correspond to each different 3 circuits; NP: non-pulsatile pressure; Pm: mean pulsatile pressure; Ps: systolic pulsatile pressure, Pd: pulsatile diastolic pressure; PP: pulse pressure; ($p<0.001$).
Pulse pressure was higher at P5 with position I, compared to position II & III. Pm was higher at P5 compared to NP with position I.
N.B. For further details please refer to the following experimental movies site:
http://www.nourmd.com/

Table 5. Results of momentum energy losses, obtained in 3 different mock circuits.

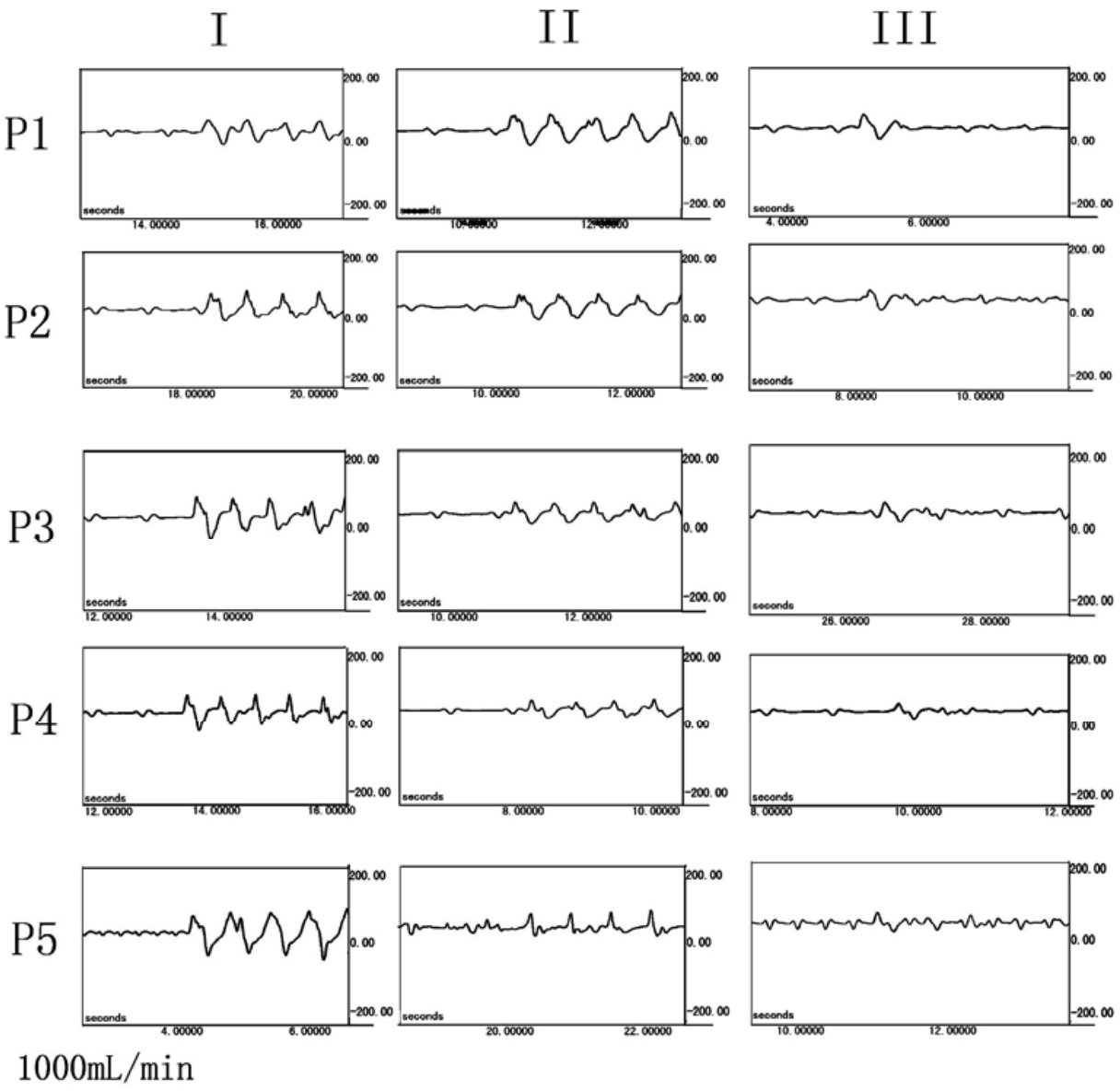
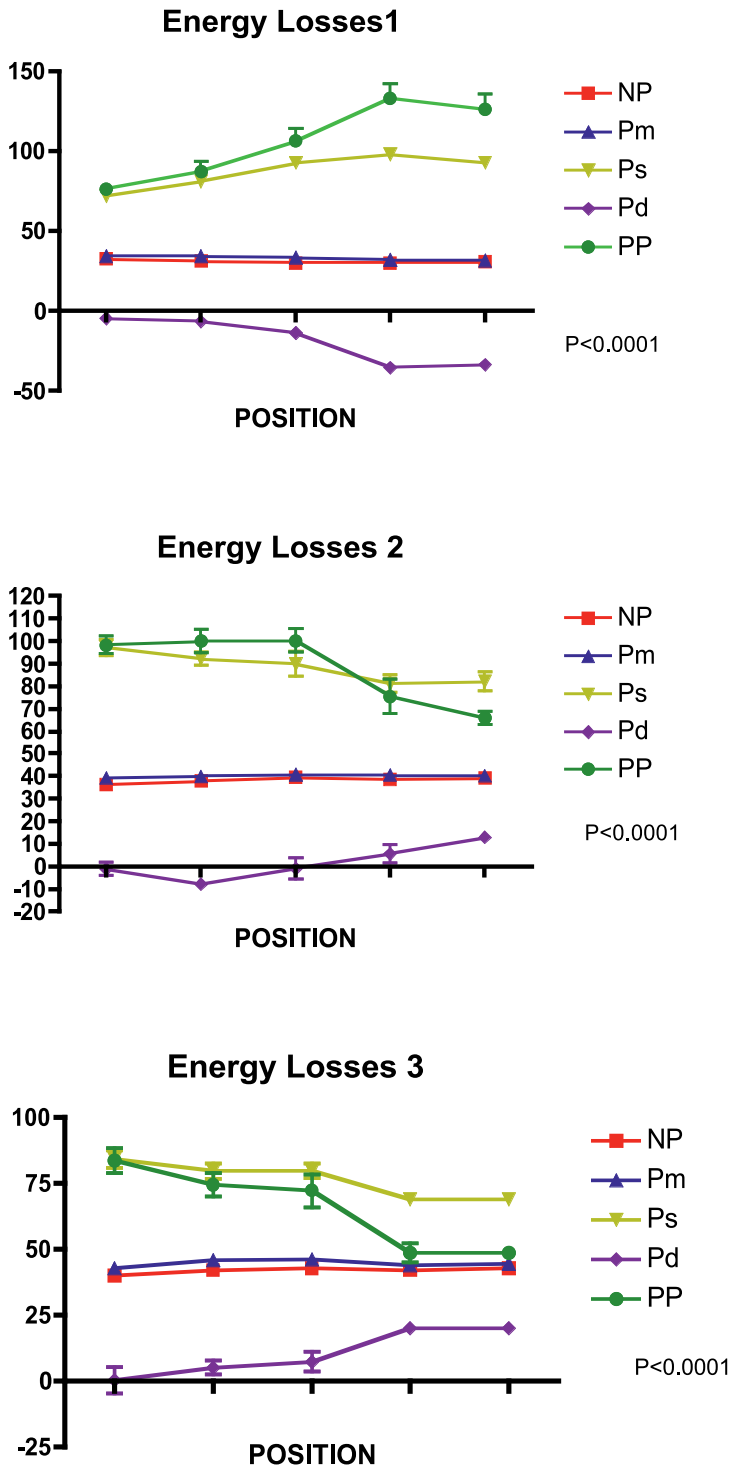


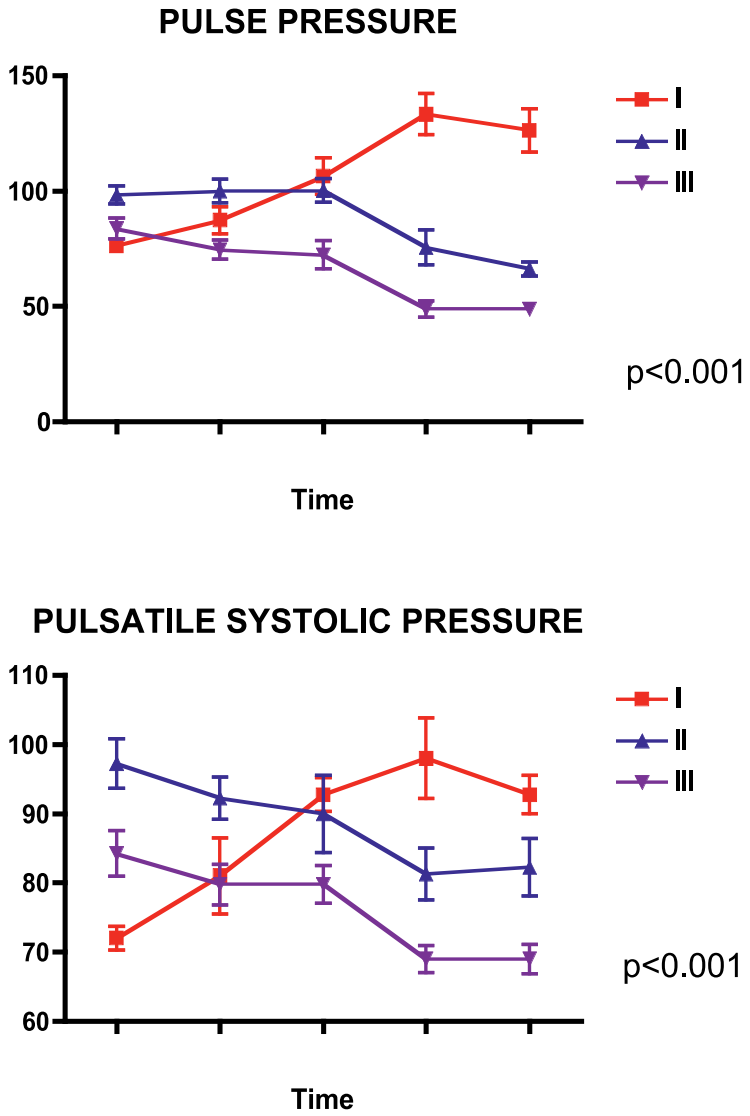
Fig. 16. Perfusions curves obtained in vitro

Perfusion curves (in mmHg) obtained at different circuit sites in 3 different pulsatile Tube positions: I, II, III close & distant from aortic cannula and pre-oxygenator respectively. The perfusion curve amplitude was significantly higher at P5 with position I, compared to positions II & IIII.



Energy losses 1 (upper panel) = pulsatile tube at 6 cm from aortic cannula; Energy losses 2 = pulsatile tube at 150 cm from aortic cannula; Energy losses 3 = pre-oxygenator pulsatile tube position. P1-P5 = distant circuit spots for perfusion pressure records (mmHg). NP= non-pulsatile; Pm = mean pulsatile pressure, Ps = systolic pressure; Pd = diastolic pressure; PP = pulse pressure. The pulse pressure (green color) was significantly higher with position I compared to positions II & III.

Fig. 17. comparative steady and pulsatile flow perfusion curves obtained from 3 different circuits



Energy losses with different tube positions: I = pulsatile tube at 6 cm from aortic cannula; II = Pulsatile tube at 150 cm from aortic cannula; III = Pulsatile tube pre-oxygenator. P1-P5 = perfusion pressure records (mmHg) at main circuit energy losses spots. At P5 the pulse pressure (upper panel) as well as the systolic pressure (lower panel) were significantly higher in position I (red color) compared to other positions: II (blue color), and III (violet color).

Fig. 18. Pulsatile flow pulse pressure (upper panel) and systolic pressure (lower panel8)

7.1.5 Comments

In this study, a steady perfusion flow was transformed successfully into pulsatile flow with a simple double lumen tube integrated into the arterial perfusion line of a conventional CPB circuit. According to our previous explanations (Figures 4 and 8), quantification of circulatory perfusion devices (CPB, CAD) depends on their momentum energy losses. The Bernoulli's principles of energy losses could be applied with accuracy in vitro to quantify lumped models like CPB (Undar et al., 2007). In vivo vessels elasticity and vascular tone bring CPB quantification more closer to Newton's law of shear stress as a major stimulant for endothelial NOS / resistances control.

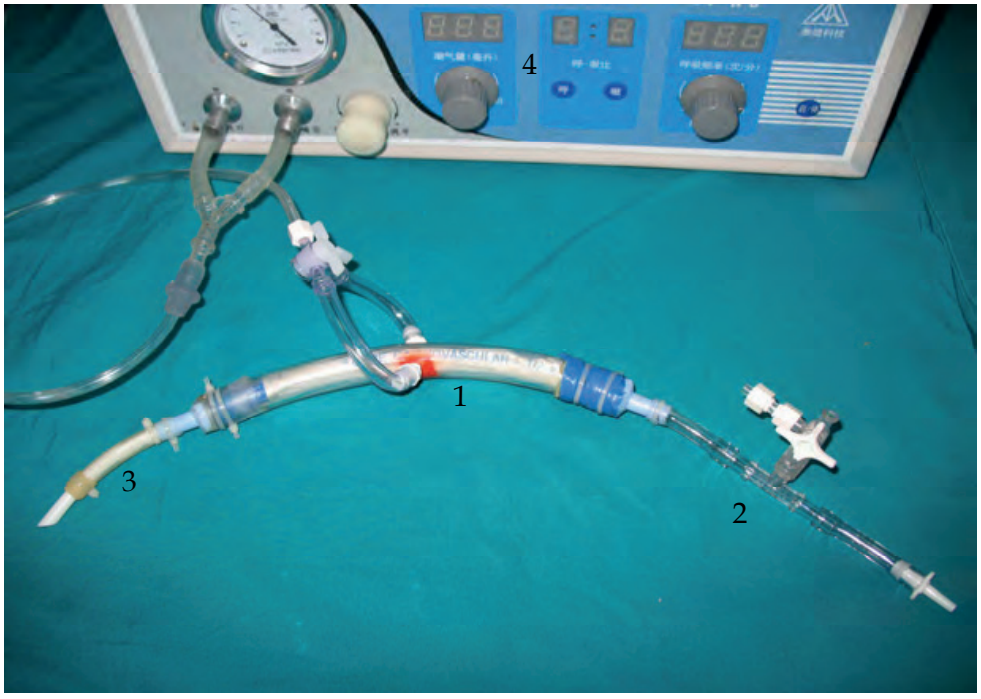
The resulted energy losses have proven the importance of the pre-cannula zone represented in position I by P4, compared to P3 and P2 with positions II and III respectively showing severe turbulent flow with important vortices constitutions at this zone or (Z 3). Finally, the prototype by its position downstream to oxygenator could avoid an important obstructive zone of energy losses, which is almost constant with current CPB necessitating a double perfusion pump system and special low resistance oxygenator.

Conclusion CPB induces momentum energy losses with severe endothelial dysfunction. Current pulsatile devices induce inadequate curves with high costs. Pulsatile tube, adaptable to a conventional driving system could induce homogenous, downstream and nearly physiologic pulsatile perfusion flow with low momentum energy losses. This is a cost-effective method, promising low mortality and morbidity, especially in fragile cardiac patients.

7.2 In vivo study (study in progress)

The pulsatile tube device was tested as a left ventricular assist device (LVAD), in pediatric animal models (piglets) with acute myocardial ischemia.

Materials and methods: in the pulsatile group: a prototype of a pulsatile tube was realized in the same manner as the in vitro study, then a short piece of 14 Fr. PVC tube was modified as a aortic cannula (Figure 19), in a matter to avoid the conastant energy losses caused by current cannulae length with narrow tips. Same a small LV vent was attached to the other end of the tube. The whole system was connected to a pulsatile generator console (HX-300 TaiMeng Technologies Inc®). In the control group: a centrifugal pump (Sorin group Revolution ®), was connected to a standard aortic cannula (12 Fr. DLP®-Medtronic, Inc.) and apical vent (14 Fr. DLP®-Medtronic, Inc.).



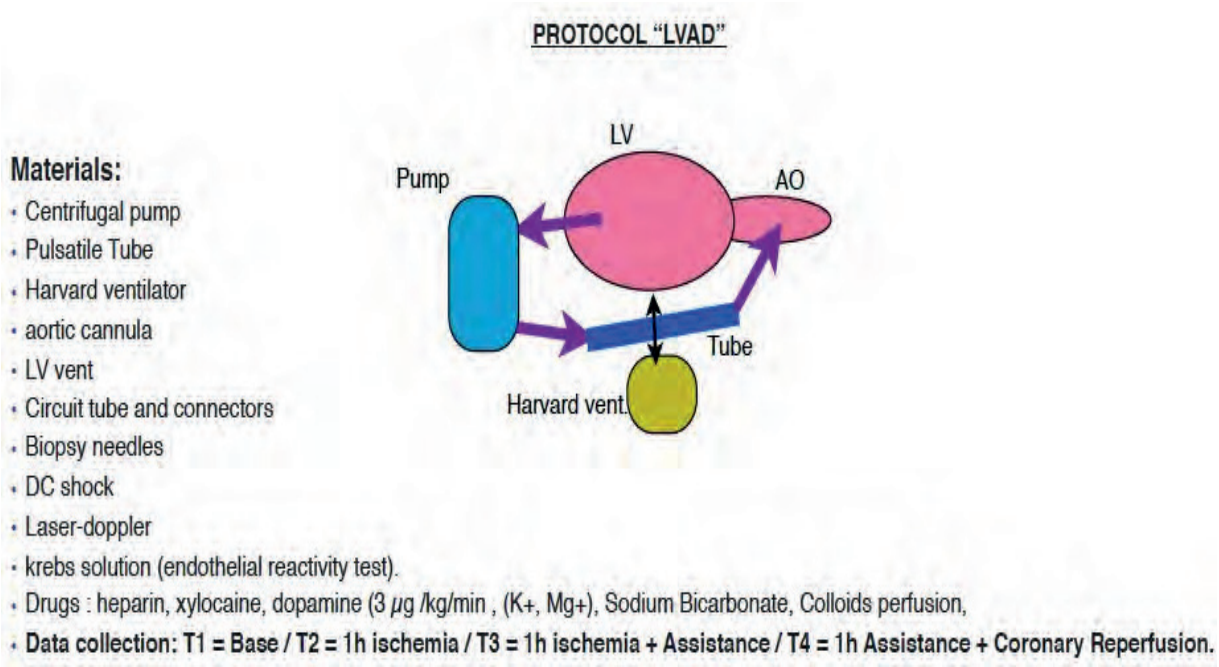
Tube (1) is connected to aortic cannula (2), LV vent (3) and console (4).

Fig. 19. Pulsatile tube prototype used as LVAD

Steps	Maneuvers
1	Anesthesia / sternotomy / pericardectomy / dissection of great vessels.
2	Insertion of an infundibular Swan-Ganz, aortic and apical pursestrings.
3	Hemodynamic measurement / blood test data for Time 1 (T1).
4	Heparin injection (2ml/kg) LAD coronary artery mid-term ligation (snugger).
5	Time 2 (T2) = after 1 hr of ischemia without any medical support
6	LVAD System switched on for 1hr.
7	Time 3 (T3) data collection after 1 hr of assistance with LAD ligation.
8	Removal of LAD snugger (coronary reperfusion + LVAD assistance) for 1hr.
9	Time 4 (T4) data collection before animal sacrifice

Table 6. Summary of the surgical steps

Operative schema and steps of surgical protocol are resumed in (Figure 20) and (Table 6) respectively.

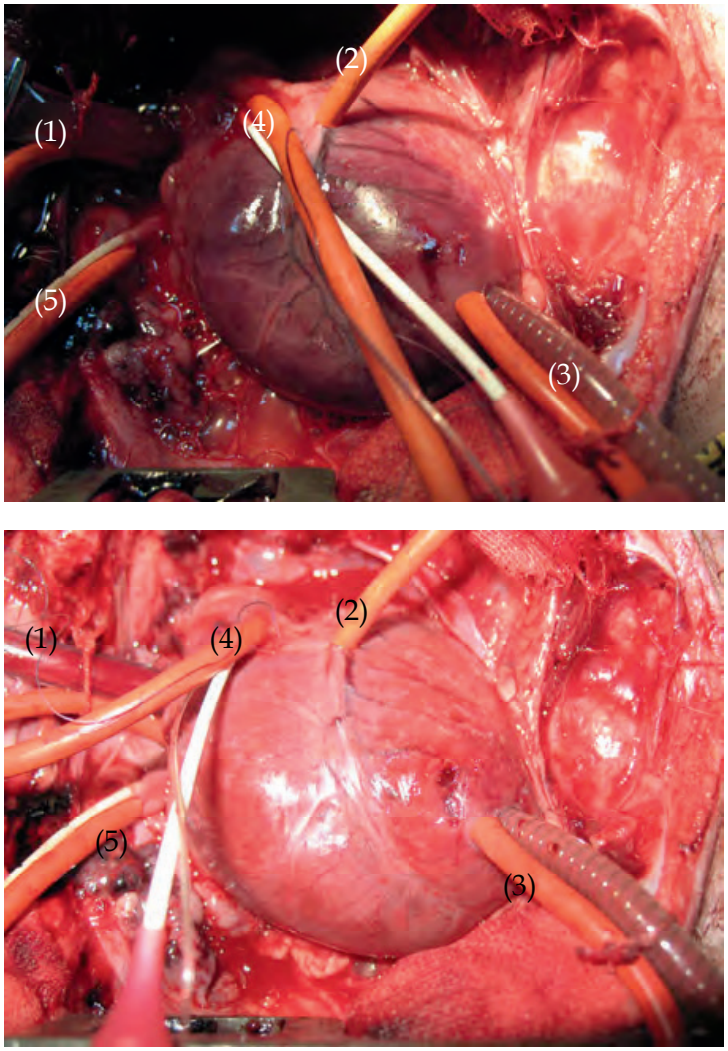


(Ao=aorta, LV=left ventricle, vent. = ventilator)

Fig. 20. Schema representing the pulsatile tube as a LVAD

7.3 Results

This ongoing study results showed better hemodynamic with lower cardiac enzymes in the pulsatile group compared to control (Figure 21) and (Table 7).



Upper panel: shows a massive myocardial ischemic zone after LAD ligation; Lower panel: ischemic zone after 15 min of pulsatile tube assistance. 1 = Aortic cannula; 2= LAD snugger (permanent coronary occlusion); 3 = left ventricular apical vent; 4 = trans-infudibulum pulmonary artery & Millar right ventricular pressure catheters; 5 = right atrium pressure line.

Fig. 21. Pulsatile tube as LVAD in piglet ischemic model

Test	**T1**		**T2**		**T3**	
	P	**NP**	**P**	**NP**	**P**	**NP**
cTnT*	0.036	0.06±0.07	-	021±0.1	0.029	1.31±0.61
CK-MB*	0.92	0.56±0.41	-	0.89±0.85	0.100	100±4
PLT	351	487±100	-	245±128	47	80±3
Htc	0.27	0.32±0.06	-	0.28±0.08	26	33±7
Lac (v)	1.23	3.3±3.1	-	4.9±4.1	0.6	0.4±0.1

Table 7. Biochemistry results: cardiac enzymes*; P: pulsatile group; NP: non-pulsatile (control group); Plt: platlets: Htc: hematocrit; Lac (v): venous lactate. T1: baseline; T2: 1h of ischemia; T3: after 2h of myocardial assistance.

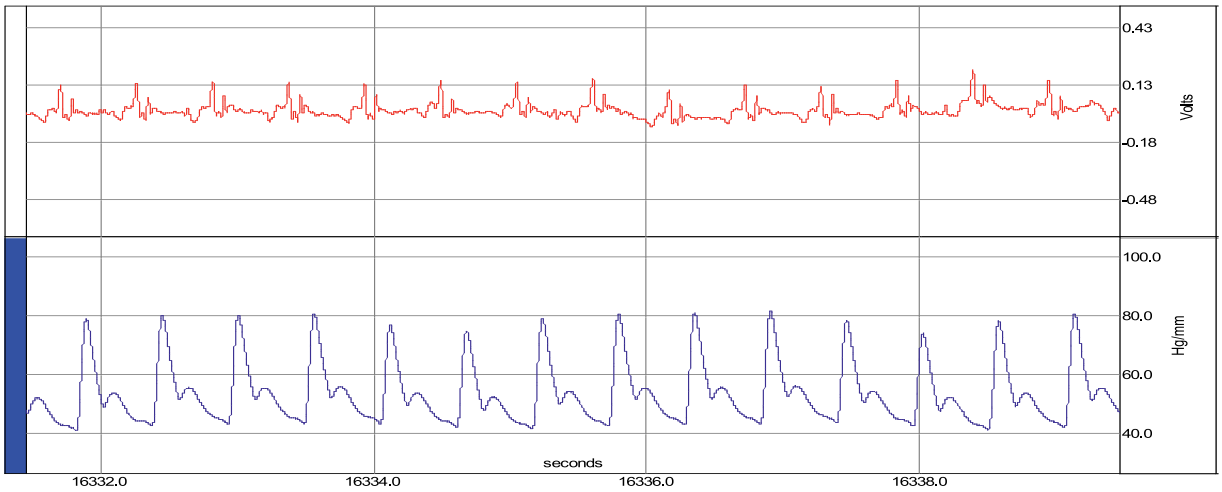


Fig. 22. Pulsatile tube perfusion curve in vivo, as a LVAD in acute MI piglet

The pulsatile tube's perfusion curve was nearly physiologic with complete discharge of the LV and unsynchronized with heartbeatt, as have been demonstrated on the operative movies.

7.4 Operative movies of the pulsatile Tube (LVAD):

- Pulsatile as a LVAD associated with a conventional roller pump (Cobe® Cardiovascular Inc.): http://www.nourmd.com/
- Pulsatile tube as a main LVAD, without any other associating driving systems: http://www.nourmd.com/
- Control group movie, LVAD by (Sorin Group Revolutionary centrifugal pump®): http://www.nourmd.com.

7.5 Comments

The exposed results proved the feasibility as well as the effectiveness of the pulsatile tube as a LVAD. These preliminary results have shown hemodynamic improvement and myocardial recoveries, lower cardiac enzymes in the pulsatile group, compared to control. This hemodynamic improvement was significant in the pulsatile tube group and despite the maintained coronary obstruction in a fragile pediatric model, with very poor coronary collaterals. Interestingly we've tested the tube alone without a perfsuion pump and LV vent, as an endocardial stimulator. Myocardial recovery and macroscopic disappearance of the ischemic zone were obvious after few minutes (< 5min), of unsynchronized pulsations (please refer the attached movie). This was ended by severe vasodilatation and cardiac arrest. Currently, we are trying to overcome these drawbacks, particularly, the inner tube (PTFE) microporosity and vasodilatations, with a new generation of pulsatile tube prototypes.

8. Evaluation of the pulsatile catheter device (in vivo)

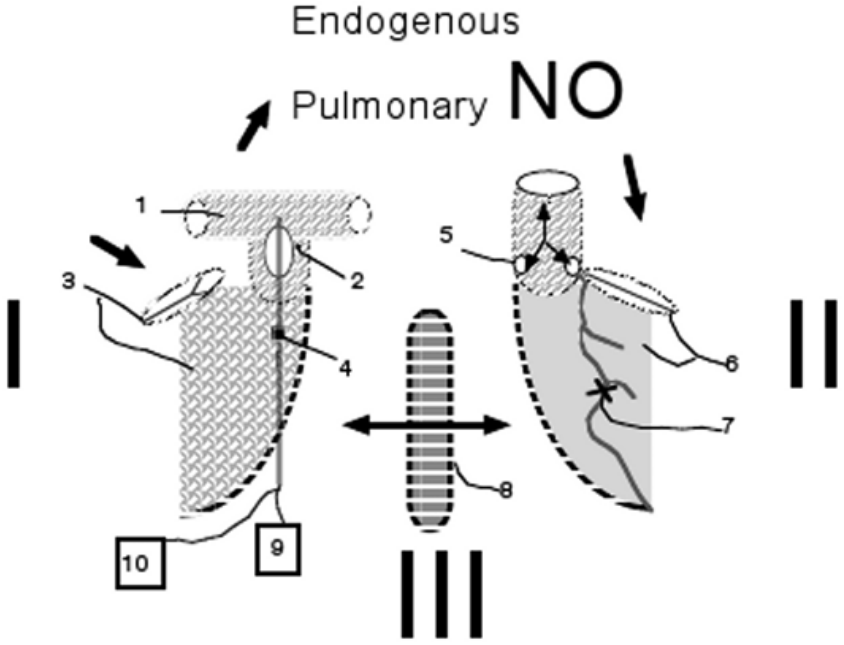
Prototype: a standard IABP catheter (8 Fr., 30 cc) was modified. Briefly, its original balloon membrane was peeled off and replaced with a small piece of commercial rubber balloon, secured and tied manually at each end of the catheter. This created an inflatable

compartment of 1×1 cm. The distal part of the prototype was connected to a cardiorespiratory monitor (BIOPAC® physiology monitoring system, ECG channel). For a pneumatic rhythmic driving force, it was attached to a small animal ventilator (HX-300 TaiMeng Technologies Inc®). It was tested for leakage while pulsating in a heparinized saline bath. Once the prototype was inserted into the pulmonary trunk, the circuit inflation volume was adjusted (usually between 50-90 ml) to avoid right ventricular outflow tract obstruction. The ventilator was pulsed at a frequency of 110 cycles/min. The prototype device was tested in two animal model studies for acute MI and acute PAH as follows:

8.1 Acute myocardial ischemia model

(part of the results was presented at the 17th conference of ACTVS, Nour, 2009)

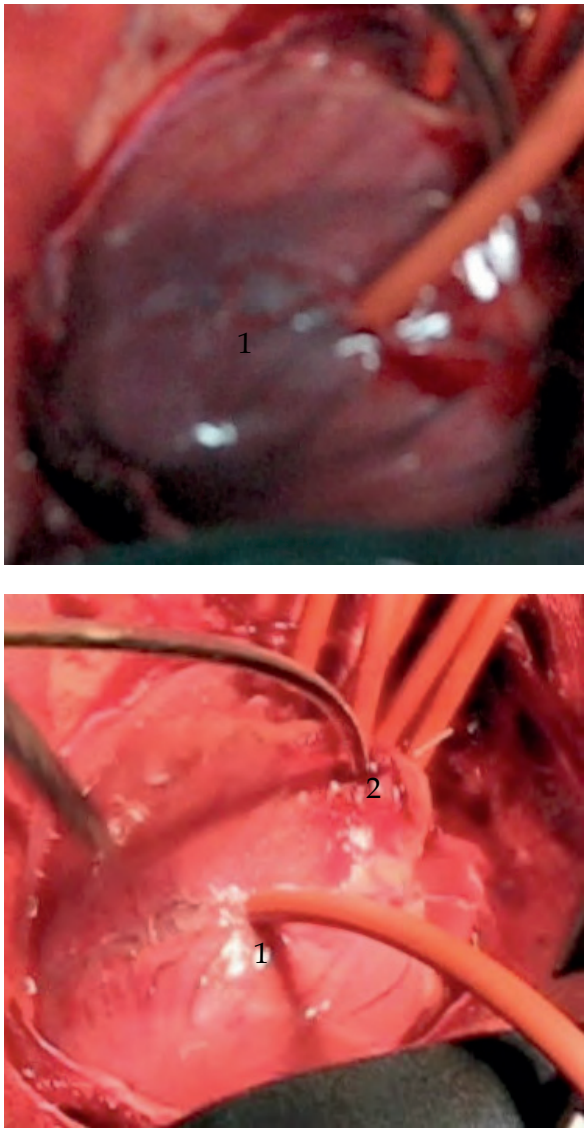
Material and methods: Twelve piglets (8.3 ± 1.5 kg) were given either pulsatile (P: n=6) or non-pulsatile (NP: n=6) nitrates treatment. Both groups underwent permanent left anterior descending coronary artery (LAD) ligation with a median sternotomy (Figure 23). After 1 h of ischemia, heparin was injected (150 IU/kg). In group P, a prototype CAD, driven by a small ventilator, was introduced into the pulmonary trunk and pulsated intermittently over 1 h at 110 bpm, irrespective of heart rate (73 ± 16 bpm). In group NP, nitrates were given (7±2 μg/kg/min) for 1 h. Animals survived ischemia for 2 h in group P vs. 93±30 min in group NP.



1 = Pulmonary artery (PA); 2 = pulsatile catheter fitting PA trunk; 3 = right ventricle (RV) inlet-outlet compartments; 4= infundibular site of pulmonary catheter insertion; 5 = arrows showing presumed passage of pulmonary eNOS (backward through coronary ostia and/or forward through systemic circulation); 6 = left ventricle (LV) inlet-outlet compartments; 7 = permanent ligation of the left anterior descending coronary artery distal to the second diagonal branch; 8 = interventricular septum; 9 = cardiorespiratory monitor; 10 = pneumatic driving force. I = pulmonary eNOS primarily induced at PA zone with catheter pulsation; II = pulmonary eNOS natural passage through the left heart circuit; III = presumed pulmonary eNOS involvement in myocardial recovery most probably through microcirculation and/or the RV interseptal coronary network.

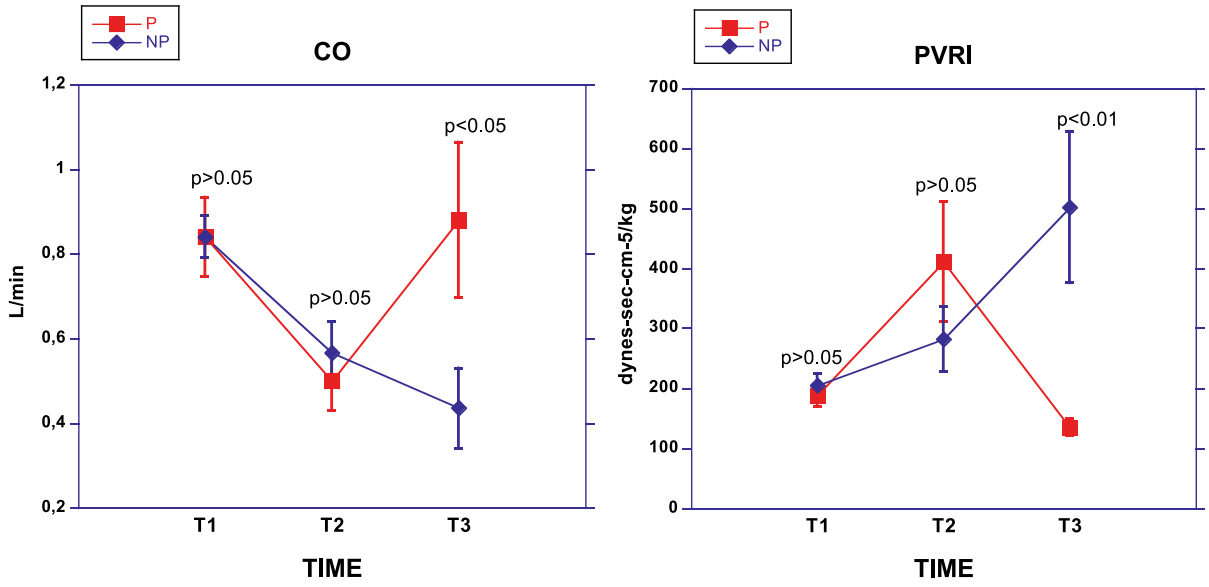
Fig. 23. Presumed mechanism and passage of induced pulmonary eNOS

With the macroscopic disappearance of infarction (Figure 24), group P exhibited improved hemodynamics (Figure 25) and significantly lower myocardial apoptosis (0.66±0.07) compared to group NP (4.18±0.27), (Figure 26). Vascular resistances (dyne.sec/cm^{-5}.kg^{-1}) were significantly lower (P<0.01) in group P vs. group NP: pulmonary resistance was 119±13 vs. 400±42, and systemic resistance was 319±43 vs. 1857±326, respectively. Myocardial endothelial NO synthase mRNA expression (Figure 27), was higher in group P (0.90±0.09) than in group NP (0.25±0.04; P<0.01), probably due to endogenous pulmonary NO secretion.



Left panel figure showing dark infarcted myocardial after 50 min of ischemia; right panel figure showing significant reduction of ischemic myocardial zone after 10 min of pulsation; 1 = left anterior descending coronary artery snugger; 2 = infundibular site of the intrapulmonary pulsatile catheter insertion.

Fig. 24. Macroscopic disappearance of the ischmeic zone in group P



Right panel showing the pulmonary vascular resistances index (PVRI) calculated from pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at three predetermined time: T1= baseline; T2 after 1H of shunt and T3= end of 1h therapy. at T1 (baseline) and the end (T3). PVRI (dynes.sec.cm^{-5}/kg) were significantly lower ($p<0.01$) were significantly lower at T3 in group P compared to group NP. Left panel showing the cardiac output (CO) from both groups P and NP. CO (L/min) was with significantly improved at T3 in group P compared to group NP ($p<0.01$), in group P (red color) compared to group NP (bleu color).

Fig. 25. Hemodynamics improvement with the pulsatile treatment in group P

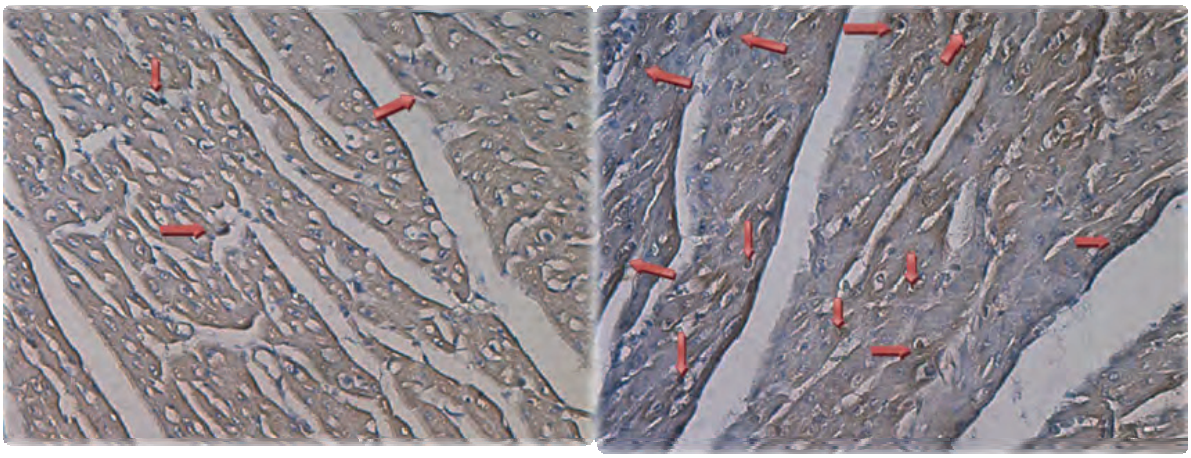
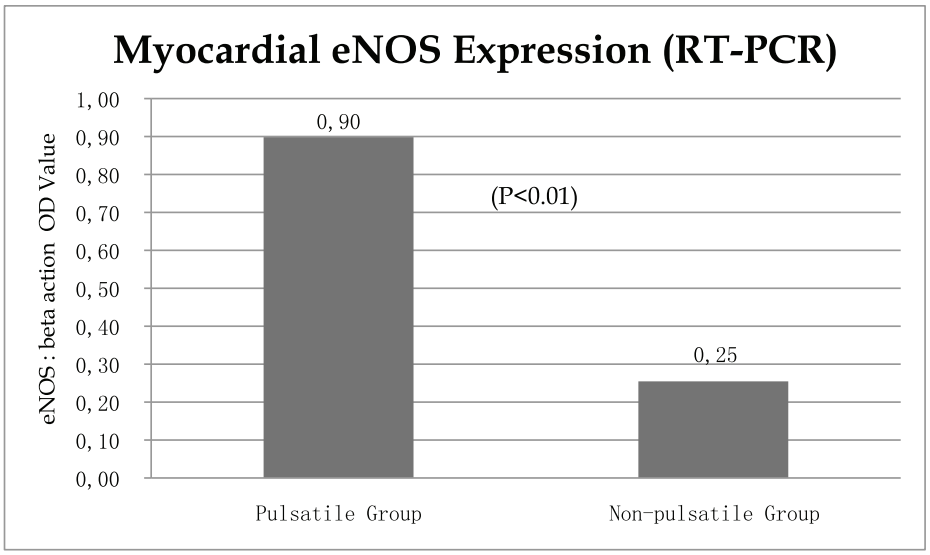


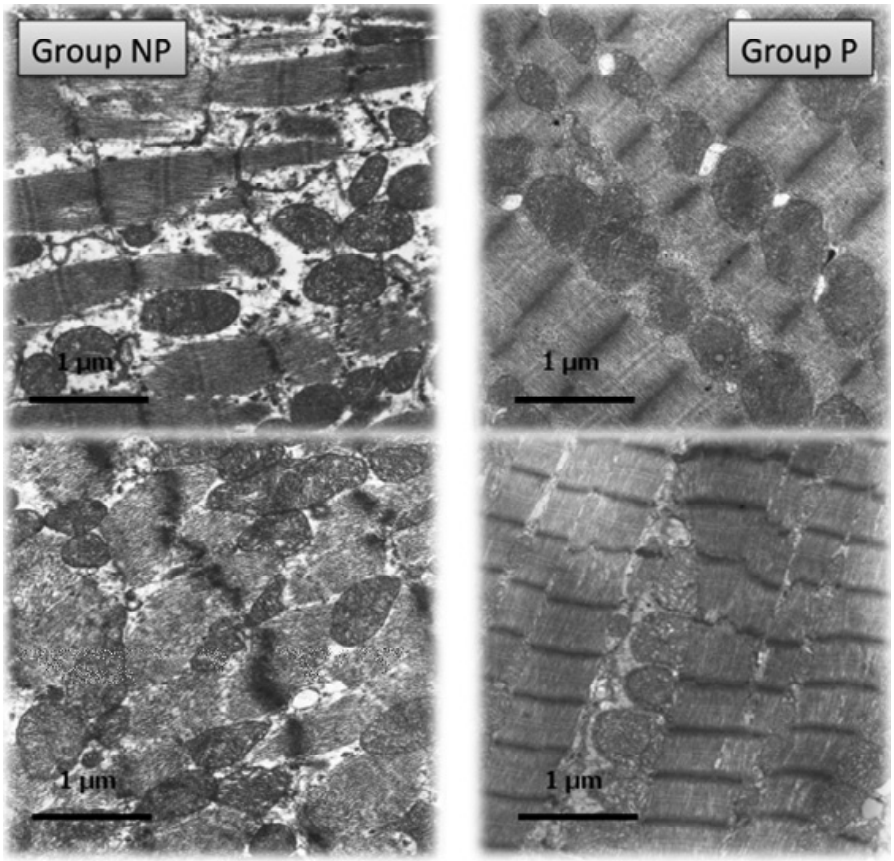
Fig. 26. Myocardial apopotosis (TUNEL test)

Representative figures from both groups showing apoptotic cells manifestations (red arrows), from both groups: group P (left) and group NP (right). The apoptotic index (AI) in group P was significantly lower than that in group NP ($P<0.01$).



RT-PCR results shown with statistics, in which myocardial eNOS expression was significantly higher in group P (left) compared to group NP (right). (p<00.01).

Fig. 27. Myocardial eNOS mRNA expression



Left panels: samples from the non-pulsatile, nitrate treatment group (NP); right panel: sample from the pulsatile treatment group (P). Notice the relatively well-preserved myocardial microstructure in group P. Bar scale on each graph equals one micrometer.

Fig. 28. Myocardial microstructure visualized with transmission électron microscopy

8.2 Comment

Decalogue of original observations emanated from the present preliminary study as follows:

i. Hemodynamic improvement, with significant recovery of the myocardial contractility and cardiac output (CO), despite maintained coronary obstruction. This was obvious macroscopically, and confirmed by low myocardial apoptosis manifestation, and relatively well-preserved cardiomyocytes organelles in the pulsatile group P.
ii. Intrapulmonary shear stress enhancement, that was induced successfully and for the first time according to literatures, as that was practiced with uncertain results, using an intra-aortic balloon pump (IABP) (Letsou et al. 1993). The uncertainty is probably due to differences between vessel geometries and catheters diameters, in addition the right heart side has specific morphological particularities that must be considered (Burton, 1954), (Huang W & Yen RT, 1998).
iii. Endogenous vs. exogenous nitric monoxide (NO): generally, NO has an important effects on the cardiovascular system as a potent vasodilator, inhibitor of platelets aggregation and myocardial contarctility (Jones SP & Bolli, 2006). Shear stress induces endogenous NO production by activating endogenous nitric oxide synthase (eNOS). (Chatzizisis et al., 2007), like during physical exercise Walsh et al., 2003). Also exogenously administered NO donors like Nitrates, can to be deleted induce eNOS (Ignarro, et al.,2002). Therefore, the study results showed that physiologically induced NO was superior to exogenous nitrates in acute IHD syndrome.
iv. Microcirculation vs. collaterals, in group P, the increased expression of myocardial eNOS mRNA (Depre, et al. 1997); with fewer apoptotic cells (Mital, et al., 2002) could be explained by endogenous NO due to the intrapulmonary catheter pulsation. Meanwhile the exact mechanisms of action remain to be explored. However several conditions supported the role of microcirculation, as the subendocardial resistance vessels are more sensitive to mediators of vasodilatation and endothelium dependent dilators (Pelc, 1987). In consideration of the short biological lifetime of NO (Doherty et al., 1998), and the maintained coronary ligation, the chosen model is known for poor coronary collaterals, in addition to the immature myocardium in young pig model (Gorge, et al. 1989). This may be explained by an undiscovered endothelial mediator(s) that improved myocardial microcirculation in the group P. in group P.
v. Reperfusion injury syndrome to be deleted, interestingly the study results showed that immediate myocardial reperfusion might be unnecessary. The procedure, provides stabilization as well as myocardial and hemodynamic recoveries without the urgent need of reperfusion with the well known consequences of the reperfusion injury syndrome (Heinzel, et al., 2008). This was confirmed with our ongoing study, using an intrapulmonary catheter device induced percutaneously through the jugular vein.
vi. Right heart vs. left heart endothelium, this study suggested that the right heart endothelium responded rapidly, to shear stress stimuli, compared to the left heart endothelium, which is most frequently, stimulated with devices like IABP and EECP, known for tolerance and long with long term effectiveness respectively (Pagonas, 2010). We found that the PA endothelium was hypersensitive; a few minutes of intrapulmonary pulsations were more than sufficient to drop systemic and pulmonary pressures. At the beginning of our trials, have observed severe vasodilation with

continuous intrapulmonary catheter pulsation (2 animals were expired). We then shifted from continuous to intermittent pulsation controlled by hemodynamic readings (5-10min pulsation) interrupted by pause intervals (10-15 min).

vii. Venous vs. arterial approach, the systemic arterial approach is most commonly practiced in IHD management, typically with IABP and/or PCI procedures. However, these require specific operative environments with high risks of risk vascular complications (Busch, et al. 1997); (Dangas, et al., 2001). Instead, the study provides a safer and cost-effective venous approach for IHD management that could be done by an ER therapist without the need to specific cardiac centers facilities.

viii. Diastolic CAD synchronizations vs. unsynchronized pulsatile catheter, contrarily to present synchronized cardiac assist devices (CAD), like the IABP, EECP, etc., we believe that unsynchronized catheter pulsation simplifies and broadens its application as an efficient cost-effective method for IHD management. Recorded pressure curves showed that the delivered catheter pulsation was faster than the heart rate; Nevertheless, it did not disturb right ventricular hemodynamic or obstruct the outflow tract.

ix. Suitable for almost all kinds of myocardial ischemia, as been observed, hemodynamic stabilization could be achieved after a few minutes of device pulsation without any pharmacological supports. Positioned inside the PA trunk, the device can reduce pulmonary afterload without jeopardizing preload in case of RV ischemia. Its small dimensions allow applications in pediatrics and other cases of non-atherosclerotic IHD (e.g. congenital, spasm, or vasculitis, induced MI. Moreover, in preconditioned (Bolli R, 2001), hibernating, stunned myocardial or permanent ischemic lesions (Vroom MB & van Wezel, 1996), long term intermittent intrapulmonary or intracoronary sinus catheter pulsation could restore myocardial tissues and dysfunctional endothelial coronary lesions.

x. The pulsatile catheter device vs. CAD, compared to current CAD drawbacks, an autonomous small catheter driven by a portable or implantable pacemaker-like generator, could be safely inserted into the circulatory system of any patient or chosen vessel, including arterial, venous or umbilical. And most probably, it could restore atherosclerotic endothelial lesions and endothelial dysfunction with the pulsatile catheter insertion into the intrapulmonary or intracoronary sinus in coronary atherosclerosis or into the main lumen of a diseased systemic artery (e.g. carotid, renal, femoral, etc.). An enhanced external counter pulsation studies in animal models have shown that regular application of endothelial shear stress stimuli could improve conditions related to atherosclerotic endothelial dysfunction (Zhang, et al., 2007). This could be a supportive argument for the concept.

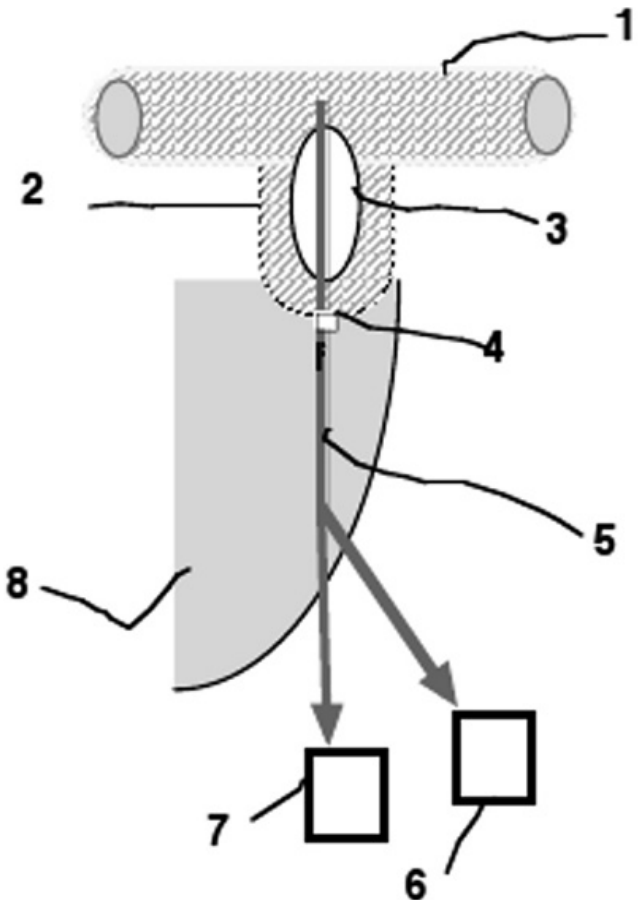
In summary, An intrapulmonary pulsatile catheter device could improve hemodynamics and recover acute myocardial ischemia efficiently, compared to nitrates. This could be induced with an appropriate intrapulmonary catheter device, adaptable to vessel geometries, regardless of coronary occlusion and irrespective of the heartbeat. The procedure represents an innovative and cost-effective method for IHD management, particularly through an intravenous percutaneous approach (ongoing study).

Operative movie site: http://www.nourmd.com.

9. Acute pulmonary arterial hypertension*

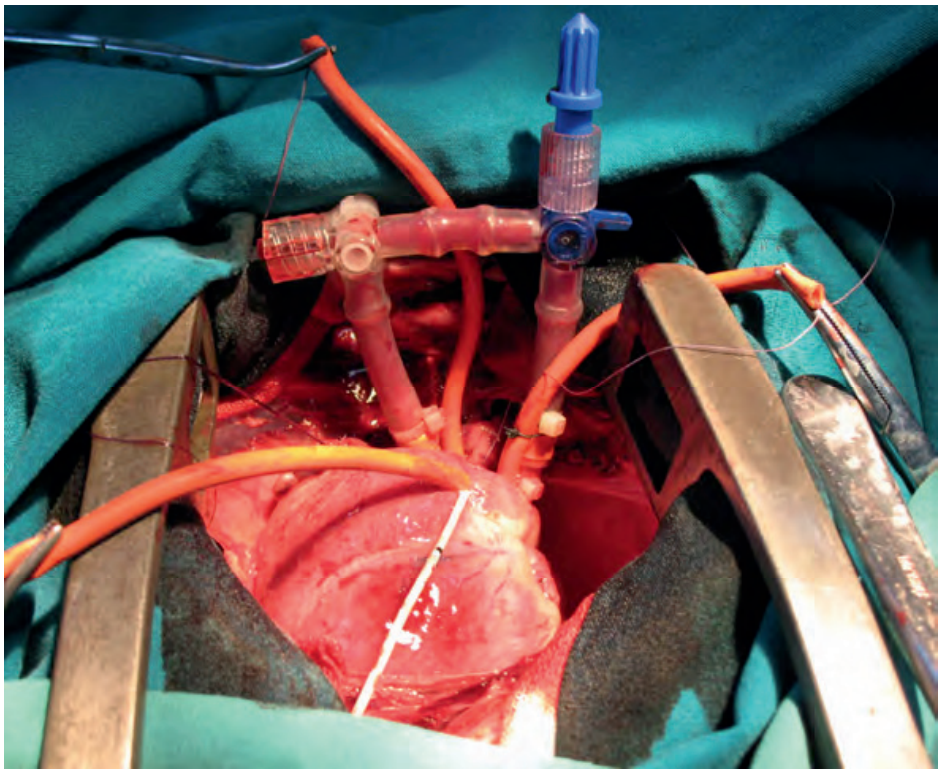
Pulmonary arterial hypertension (PAH) is a dysfunctional endothelium disease with increased pulmonary vascular resistances (PVR) and poor prognosis. Current therapies are still insufficient. Alternatively, we propose a the pulsatile catheter device as a more effective for PAH management compared to traditional treatments.

Material and Methods: *Twelve* piglets (10.3 ± 3.8 kg) were given either intrapulmonary pulsatile (P: n=6) or non-pulsatile (NP: n=6) Tadalafil treatment. After median sternotomy and heparin injection (250 IU/kg), both groups underwent aorto-pulmonary surgical shunt during 1 h then removed (Figures 29 and 30). Over a second 1 h period: in group P, a catheter prototype, driven by a small ventilator, was introduced into the pulmonary trunk and pulsated intermittently at 110 bpm, irrespective of heart rate (90.6±10.74 bmp). In group NP, Tadalafil were given orally (1 mg/kg).



1 = pulmonary artery branch; 2 = pulmonary artery trunk; 3 = inflated balloon in place; 4 = infudibular snugger; 5=catheter shaft; 6= cardiopulmonary monitor; 7 = pulsatile driving system (small animal ventilator); 8 = right ventricular cavity.

Fig. 29. Intrapulmonary pulsatile system



Assembled shunt showing: 2 PVC limbs unequally cut with ½ cm; connected together with silicone tube and equipped with 2 stopcocks and pressure lines connectors, prefilled with heparinized saline and clamped ready before insertion. Aorto-pulmonary shunt in place with infundibular intrapulmonary artery pressure line (white color).

Fig. 30. Aortico-pulmonary "U" shape external shunt system.

Statstics: Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test for eNOS and a 2-way ANOVA for hemodynamic data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

Results: hemodynamic and cardiac output (CO) were significantly ($p<0.05$) better in group P compared to group NP: CO was 0.56±0.0.26 vs. 0.54±0.11 (L/min) respectively. Mean pulmonary artery pressure (PAP) was significantly dropped in group P compared to group NP: PAP was 9.6±2.97 vs. 32.25.07 respectively. Vascular resistances (dynes.sec/cm^{-5}.kg^{-1}) were significantly lower in group P vs. group NP: pulmonary resistance (Figure 31), was 85±42.12 vs. 478±192.91, and systemic resistance was 298.8±172.85 vs. 1301±615.79, respectively. The endogenous NO synthase expression in PA segments with Western blot analysis was higher from group P (0.81±0.78) vs. (0.62±0.35) in group NP ($p>0.05$).

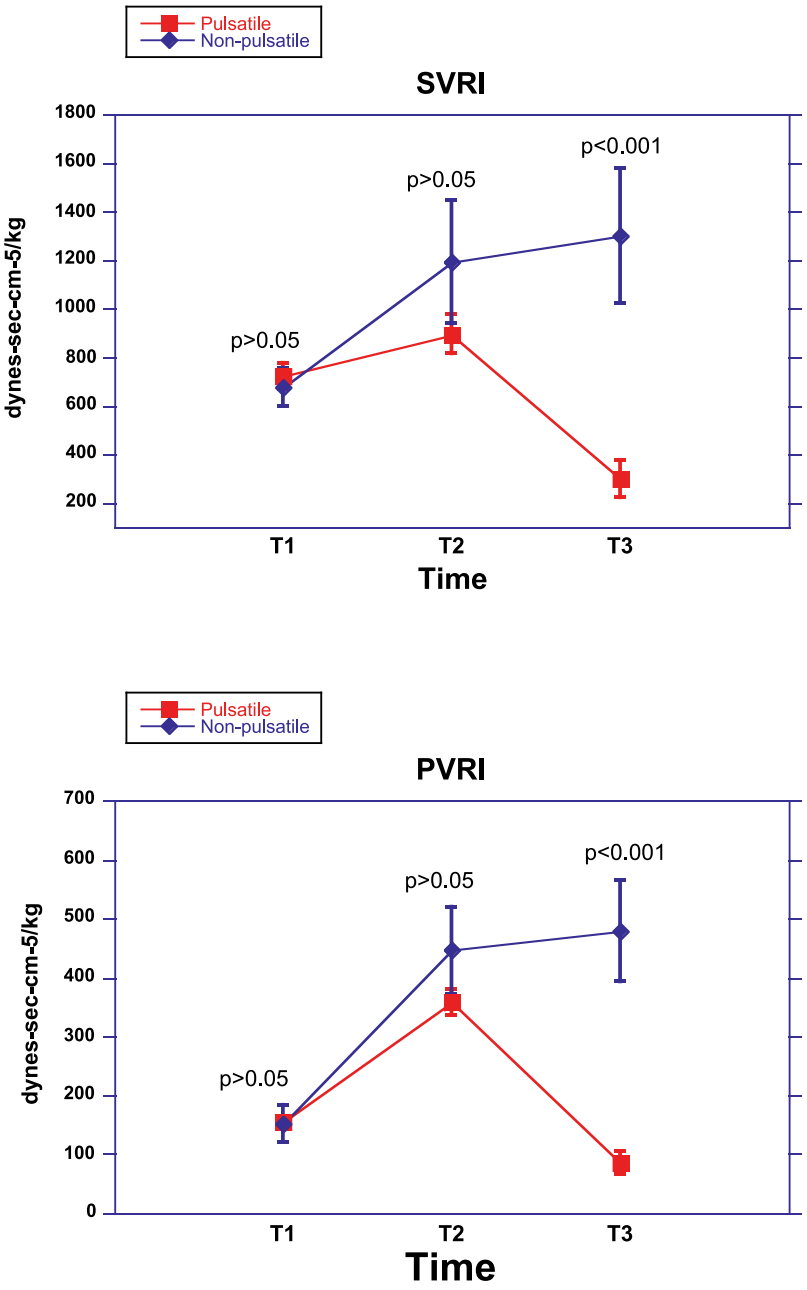


Fig. 31. Systemic and pulmonary vascular resistances indexes

Upper panel: showing data of the systemic vascular resistances index (SVRI) calculated from pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at three predetermined time: T1= baseline; T2 after 1H of shunt and T3= end of 1h therapy. at T1 (baseline) and the end (T3). Lower panel: showing data of the pulmonary vascular resistances index (PVRI) calculated from pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at three predetermined time: T1= baseline; T2 after 1H of shunt and T3= end of 1h therapy. at T1 (baseline) and the end (T3). Both SVRI and PVRI (dynes.sec.cm-^{5}/kg) were significantly lower ($p<0.001$) were significantly lower at T3 in group P compared to group NP.

Comment This study confirms the dominancy of the right heart over the left heart and hemodynamic through PVR

The effect of intrapulmonary shear stress enhancement was immediate upon both PVR and SVR in the group P. The significant improvement of hemodynamic with rapid reduction of pulmonary pressure in group P compared to the group NP, confirms the dominancy of shear stress-mediated endothelial function enhancement method over traditional therapies*. Also this confirmed what we have mentioned with the ischemic models regarding the hypersensitivity of the right heart side endothelium of the pulmonary artery compared to systemic arteries.

Conclusions: Induced with an appropriate device, intrapulmonary shear stress-mediated endothelial function enhancement, provides a more effective nearly physiological therapy for PAH.

* Abstract of the study concept was presented at the 16th conference of ACTVS - Singapore, Nour, 2008). Paper in press, submitted to the Pediatric Cardiology Journal (Nour, S 2012).
Operative movies: http://www.nourmd.com.

10. Evaluation of the pulsatile suit device

This concerns the non-invasive devices (pulsatile suit) that were tested in vivo and healthy volunteers (the author and medical doctors colleagues).

10.1 Animal model of acute RV failure*

Cardiac assists devices (CAD) for right ventricular (RV) failure remain controversial with poor results. The purpose of this study was to evaluate a pulsatile suit CAD in an acute RV failure model vs. current therapies.

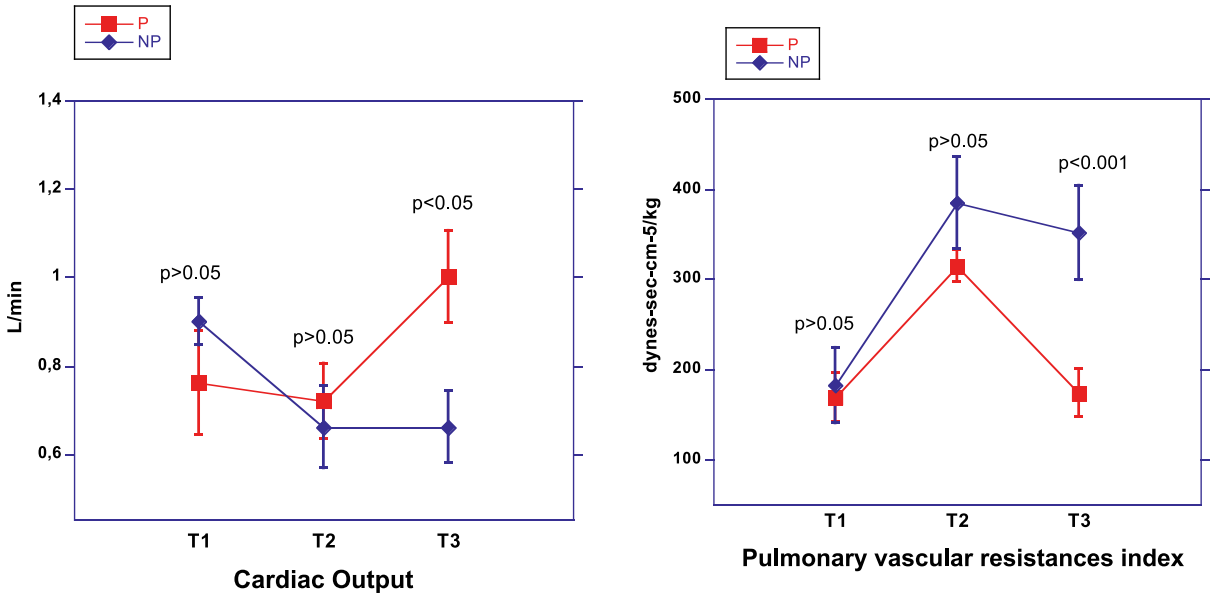
Material and methods (Figure 32): twelve piglets, divided in two equal groups: pulsatile group P and non-pulsatile group NP. Acute pulmonary incompetence was created surgically through median sternotomy. Management started once severe RV failure observed (48.1±24.5 min): in group P, a pulsatile trouser, driven by pneumatic generator was pulsated intermittently at 40 bpm, irrespective of heart rate (104±27 bmp). Group NP, was treated with oral Tadalafil (1 mg/kg), IV fluids and adrenaline (0.3µg/kg).

Results (Figure 33 & Table 8): after 1 h of therapy, hemodynamic and cardiac output (CO) were significantly ($P<0.05$) better in group P compared to group NP: CO 1±0.2 vs. 0.7±0.2 (L/min) respectively. Mean RV pressure (RVP) and pulmonary arterial (PAP) pressure were dropped in group P compared to group NP: RVP 16±6 vs. 24±2 and PAP 22±1 vs. 31±2 (mmHg) respectively. Vascular resistances indexes (dyne.sec/cm^{-5}.kg^{-1}) were dropped in group P vs. group NP: pulmonary resistance was 174±60 vs. 352±118, and systemic resistance was 611±70 vs. 1215±315, respectively. Western-blot analysis of pulmonary arteries shown higher endogenous NO synthase (eNOS) expression ($p>0.5$) in group P :0.90±0.71 vs. 0.66±0.52 in group NP.

Fig. 32. Pulsatile trouser (intraoperative view)

	Group	PAP	RVP	PVRI	CO
T1	P	24±3 / 15±2	29±4 / 14±5	168±27	0.8±0.3
	NP	23±4 /15±3	34±3 / 7±2	182±42	0.9±0.1
T2	P	41±2 / 27±3	43±2 / 16±5	314±17	0.7±0.2
	NP	42±3 / 25±2	46±2 / 12±3	385±51	0.7±0.2
T3	P	27±2 / 17±2	28±2 / 6±3	174±27	1±0.2
	NP	39±3 / 23±2	42±1 / 7±1	352±52	0.7±0.2

Table 8. Therapeutic response of the right heart hemodynamic parameters (Trouser vs. TadalafilTM): Systolic and diastolic pressures (mmHg) of the right ventricle (RVP) and pulmonary artery (PAP); PVRI: pulmonary vascular resistances index (dynes•sec/cm5/kg); CO: cardiac output (L/min); T1: baseline; T2: nearly 1 h after pulmonary valve disruption; T3: end. P: pulsatile group; NP: non-pulsatile group; ($p<0.05$).



P: pulsatile group (red color), NP: non pulsatile group (blue color); left panel showing cardiac output panel showing pulmonary vascular resistances index (PVRI); right panel showing cardiac output (CO) results obtained from both groups P and NP in three. Data were obtained from both groups (P & NP) at three predetermined time: T1= baseline; T2: nearly 1 h after pulmonary valve disruption and T3= end of 1h therapy. CO (L/min) was significantly improved ($p<0.05$) at T3 in group P compared to group NP. PVRI (dynes.sec.cm^{-5}/kg) were significantly lower were significantly ($p<0.01$) lower at T3 in group P compared to group NP. (Two ways ANOVA test)

Fig. 33. Hemodynamic figures

*Paper was submitted to the Asian Cardiovascular & Thoracic Annals Journal (in press Nour, S 2012).

Operative movies: http://www.nourmd.com.

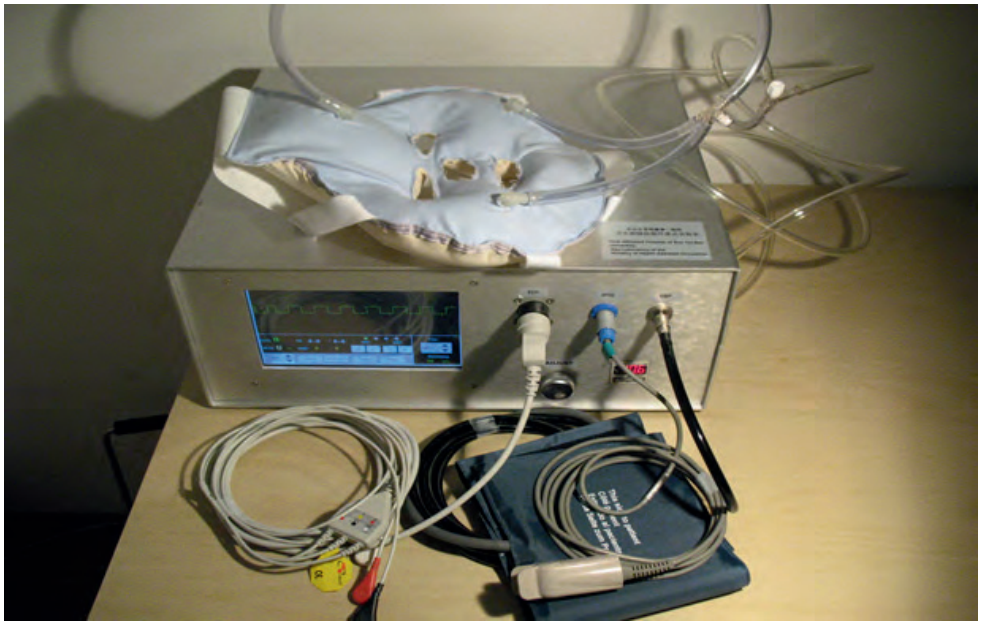
10.2 Clinical volunteers (study in progress)

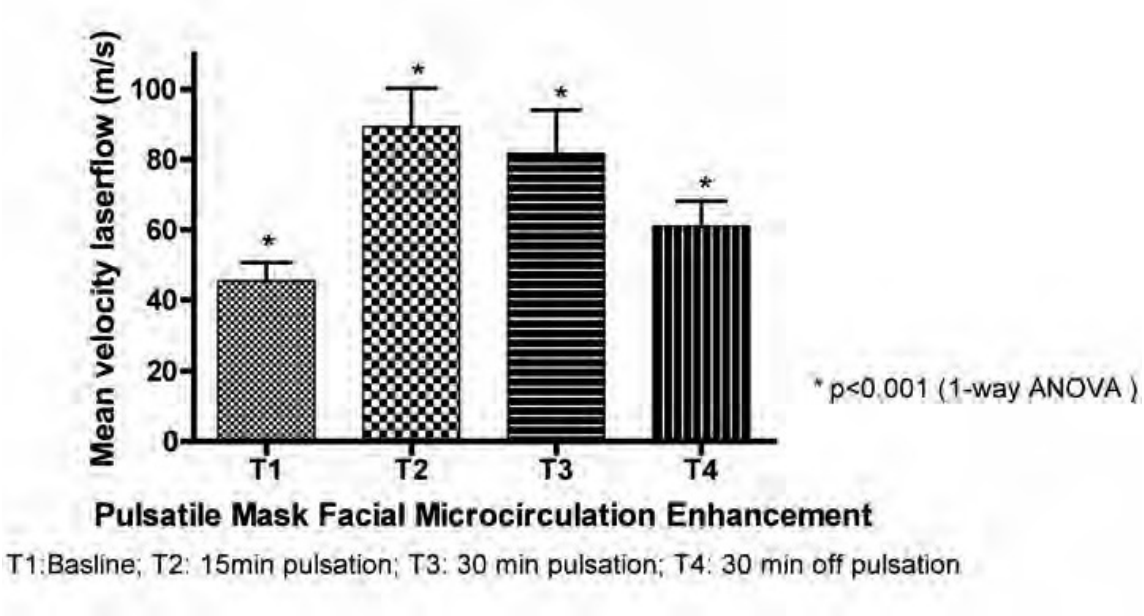
10.2.1 Mask

Pulsatile mask was tested in healthy volunteers (n=8) from both sex (age:19-68 ys), subjected to 20 minutes of low pressure (0.2-0.6 bars) pulsatile mask, synchronized with diastolic heart rate. *Statistics:* Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test hemodynamic data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

Results: hemodynamics and cerebral blood flow was significantly improved ($p<0.05$), as manifested by Doppler flow measured at the common carotid artery (Figure 35): carotid output: 246±41.73 vs. 294±50.42 (ml/min), and velocity 18±2.4 vs. 21±2.8 (cm/sec). Microcirculation measured from the tip of the nose (Perimed®-PeriScan 3 System), was

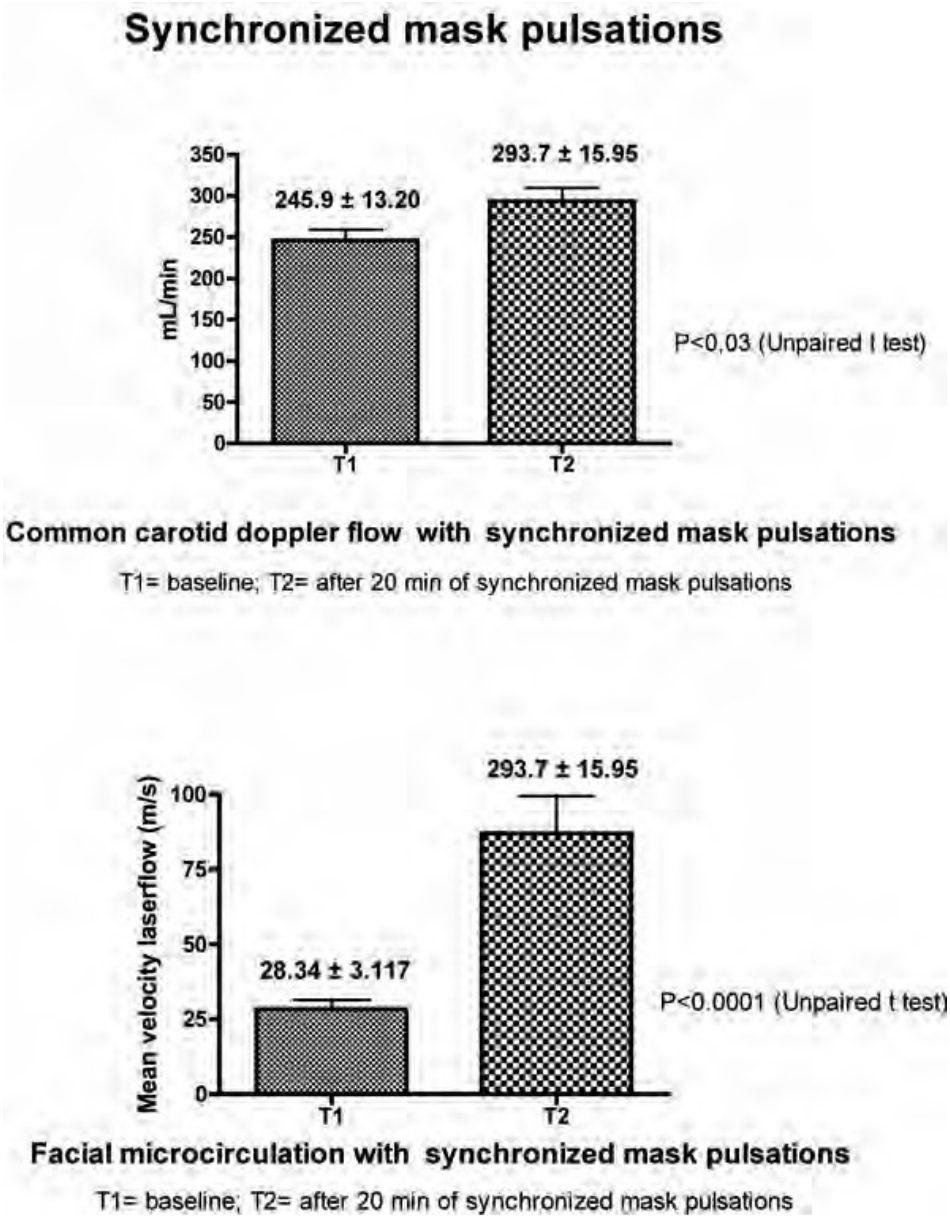
45.5±14.6 vs. 89.2±31.1 ($p<0.001$) with unsynchronized mask pulsations (Figure 34); and from the mandibular angle (measured with Perimed® - PeriFlux System 5000), was 28±12.5 vs. 87±35.2 ($p<0.05$), with synchronized mask pulsations (Figure 35).





Upper panel, showing mask device inflated and connected to a generator equipped with a set for hemodynamic measurements (ECG, BP, SaO2); lower panel showing cutaneous microcirculation measured from the tip of the nose at T1: baseline; T2: after 15 min of low pressure pulsation (0.2-0.4 bar) unsynchronized with heart rate; T3: by the end after 30 min of pulsation. T4: 30 min after the end.

Fig. 34. Pulsatile mask improving facial microcirculation



Upper panel carotid flow measured by echo Doppler; lower panel: facial microcirculation (from the mandibular angle)

T1: baseline; T2: after 20 min of pulsations

Fig. 35. Synchronized pualstile mask results

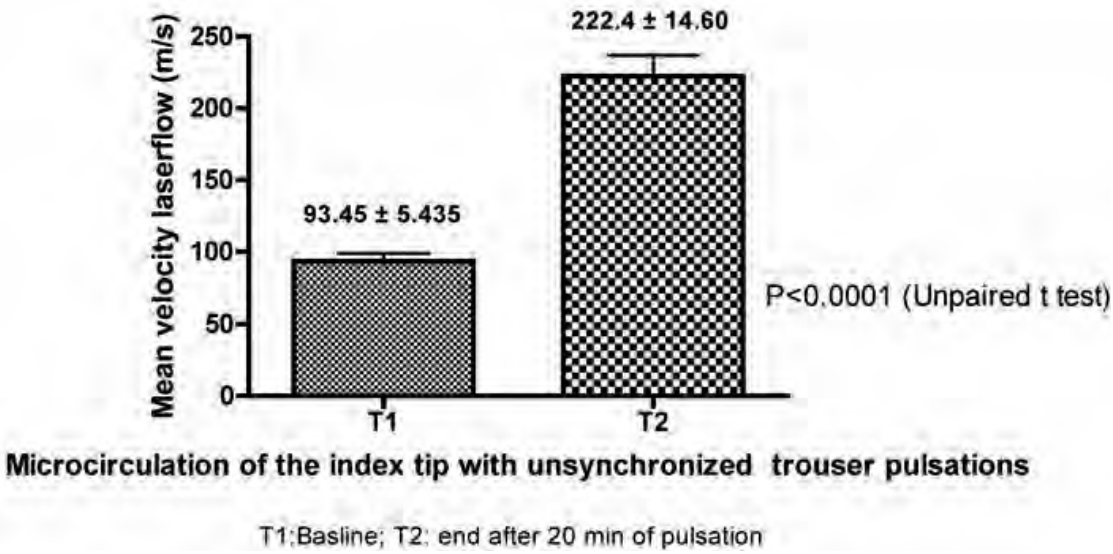
N.B. interestingly the microcirculation's flow shown in (Figure 34), was rapidly increased after 15 min of pulsations, then dropped slightly to pass in plateau over the second 15 min of stimulation. This proves the physiological effect of the device that does not stun endothelial biology, allowing self-cellular regularization in response to induced endothelial vasodilators mediators and unlikely to exogenous NO donors vasodilators (e.g. nitrates).

Movies demonstration of the pulsatile mask:

http://www.nourmd.com.

10.2.2 Trouser

Pulsatile trouser, that covering almost the trunk, was tested in healthy adult volunteers (the author and medical colleagues) (n:6), were subjected to a low pressure (1.2 bars) fixed pulsations (60 bpm) and without synchronization of heartbeat (72± 17 bpm). Results (Figure 36); after 20 min of pulsations, the peripheral microcirculation was measured with laser flowmeter (Perimed®-PeriScan 3 System) at the tip of the finger was significantly improved: 93.5±31.3 vs. 222.4±35.8 ($p<0.003$).



Upper panel: pulsatile trouser's prototype; lower pannel: increased peripheral microcirculation, measured at the tip of the right index (laser flowmeter: Perimed®-PeriScan PIM 3 System)

Fig. 36. Hemodynamic results after 20 min pulsation in 6 volunteers

Movie demonstration http://www.nourmd.com.

11. Evaluation of the Biventricular assist device "L'Orthèse cardiaque" (study in progress)

11.1 In vivo

The device was tested in an acute ischemic biventricular failure (piglet). This was created by mid ligation of the LAD, and elecrocauterization of the RV coronary artery branches, for details refer to the attached operative movies site. The preliminary results shown better hemodynamic responses with the biventricular assist device combing the pulsatile tube as a LVAD and the pulsatile trouser as RVAD (Figure 36).

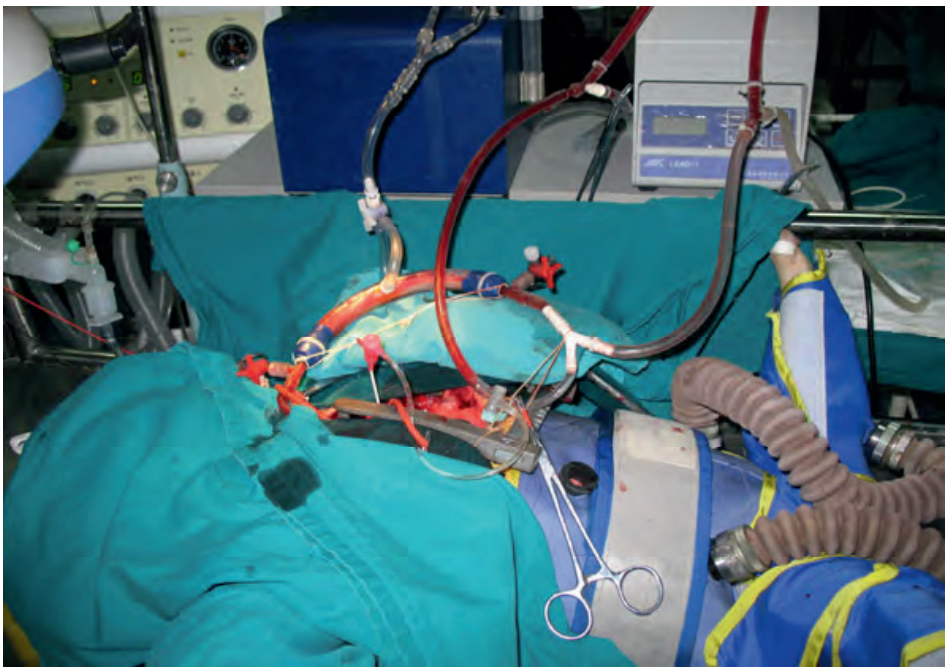


Fig. 37. Biventricular CAD (l'Orthèse cardique) in ischemic model (piglet)

Operative movies: http://www.nourmd.com.

Comment: in this study the device (l'Orthèse cardiaque) was tested as well in total cardiac arrest followed and acute ischemic biventricular failure and cardiogneic shock. The device was successfully capable to circulate the stagnant blood columns within the respect of the biophysical conditions of each heart circuit biophysiological conditions (please refer to the attached movie). The study pending new pulsatile tube constructions. The object is to maintain circulatory flow dynamics and cellular metabolism in case of acute biventricular failure until improvement of hemodynamic or arrangement for heart transplants with compatible donors in nearly physiological condition.

11.2 In clinical volunteer

The pulsatile trouser was indicated in a CHF patient, (a medical consultant from the UK), as an ultimate therapeutic option, according to a consensual patient's request. The patient was short-listed for both heart and kidney transplant, then been removed due to severely deteriorated hemodynamics: EF ≈ 15%, systolic pulmonary arterial pressure >65 mmHg,

and elevated BNP (1100 pg/ml). He was on renal dialysis (6 days/ week), chronic constipations and oxygen sleep dependent. The pulsatile trouser was applied for 2O minutes daily, in a posture position* with fixed frequency (40 bpm), irrespective of patient's pacemaker (78 bpm) and low inflation / deflation pressure (1.4 bar). The patient recovred regular bowl, and became less dependent on oxygen during the first week of treatment. After two months there was hemodynamic improvement: EF≈ 20%; systolic PAP ≈ 41mmHg and BNP ≈ 500 pg/ml. The patient reintegrated the NHS transplant program. Despite, hemodynamic improvement, the procedure was interrupted because a cholecystectomy was urgently, needed for biliary lithiasis, which may promote to shower pancreatitis with the trouser pulsations.

*N.B. In CHF patients, it is preferred to apply trouser therapy in a posture position, rather than supine position to amplify the gravity effect as an enhancement factor of shear stress with more voluminous columns of venous capacitance.

Movie demo: http://www.nourmd.com.

11.3 Comment

These aforementioned preliminary results have proven the feasibility of the concept as a promising therapeutic approach for CVD. On other word, proven the efficiency of the right heart endothelial reservoir as a physiological therapeutic backup compared to optimum traditional therapies in addressing acute cardiogenic shock state.

The pulmonary endothelium, stimulated with a small size pulsatile catheter that can be introduced intravenously and percutaneously, open a new era in cardiology as almost all types of ischemic heart disease as well as pulmonary arterial hypertension (PAH). Macroscopic disappearance of the ischemic zone confirmed with low myocardial apoptosis and that despite permanent ligation of the coronary artery means improved hemodynamic is more related to open myocardial microcirculation in neonate animal model known with poor coronary collaterals.

A significant drop in the pulmonary vascular resistance was the key of hemodynamic improvement. This can be induced with the proposed pulsatile systems after short period of intermittent shear stress-mediated endothelial function stimulations at the splanchnic and hepatic venous capacitance, or at the pulmonary artery, and irrespective to heart rate.

Pulsatile suit concept results that have been obtained in volunteers also open a new era of therapeutic approach in nearly all types of endothelial dysfunctions pathogenesis as follows: with (Type A), endothelial dysfunction with heart disease patients; in Type B, with endothelial dysfunction and normal heart function (e.g. diabetic, systemic arterial hypertension, PAH, erectile dysfunction, etc); and Type C, as prophylactic in healthy individuals, liable for endothelial dysfunction pathogenesis (Astronauts, bedridden, etc) as well as a circulatory hemodynamic physiological stimulus (e.g. athletics, anti-aging, etc).

The pulsatile mask can improve the cerebral circulation directly through the cavernous venous systems, and systematically through the jugular vein system, current studies show enhancement of the retinal artery flow as well as diameter, which ca be effective in treating early neurodegenerative diseases and stroke patients.

This improvement is observed at points remote from the pulsating zone, i.e. where the suit was being worn.

A clear improvement in microcirculation has also been observed at the fingertips as a result of putting a pulsatile suit (trouser) on the bottom portion of a patient's body as shown in (Figure 36).

Practically, delivery of shear stress stimuli at the compliant pulmonary artery (PA) zone (zone5), can be induced according to the Bernoulli's principles with a small size pulsatile catheter adaptable to the pulmonary trunk geometries for shear rates enhancement at the inner boundaries layers, irrespective of heartbeat without obstructing the right ventricular outflow tract. Meanwhile at the superficial venous capacitance (zone1) shear stress enhancement could be achieved externally with the pulsatile suit.

At the left heart side, an endothelial shear stress will be induced by the pulsatile tube. The pulsatile tube could adapt whether a conventional CPB or CAD, provides a nearly physiological pulse pressure with lowest momentum energy losses, particularly in association with the Smartcan. It will considerably reduce the distance between CAD and the perfused artery (Z3).

Similarly, an improvement in the microcirculation of the myocardium has been observed in an ischemic model by permanent ligation of the left anterior descending coronary artery (LAD), after applying shear forces generated by pulsatile catheter inserted in the pulmonary artery forming part of the right circuit of the heart.

Given the very short lifetime of nitric oxide, it cannot reach zone that are remote from the site where it is secreted, since it is necessarily absorbed by hemoglobin before reaching said remote zones. Thus, it has been found that at least one mediator mechanism other than those that are already known and secreted by the endothelium is capable of triggering the opening of microcirculation. The devices and methods of the present concept advantageously enable such secretion to take place.

As a priority, assistance should be provided to the right portion of the heart. It is known that the right heart "dominates" the left heart and controls hemodynamics by pulmonary resistances (Nour S 2008). Isolated ventricular assistance, on the left or right, can then be envisaged in accordance with the present disclosure; and after that assistance for the left heart.

The method makes it possible to restore the endothelial function progressively by maintaining quasi-physiological shear forces on the endothelium; consequently, there is a significant improvement in the function of myocardium, thus making it possible avoid subsequent transplants.

Alternatively, the pulsatile catheter prototype, when applied in the clinic, could be implanted into the pulmonary artery through a central venous line (ongoing study), in hospital settings, it could be connected to a small portable-implantable driving device. Patients with catheter device set implants would benefit from real-time hemodynamic measurements and simultaneous therapeutic pulmonary pulsation. Thus, this approach promises to be cost-effective.

By providing immediate improvement of myocardial microcirculation, the device could become a first priority in IHD as well as PAH managements.

In future investigations, the device could be inserted through the PA (ongoing study) or coronary sinus, either associated or not with an absorbable stent, to test for enhancements in the restoration of endothelial function.

Over the long term, shear stress-induced endothelial regulation, alone or in combination with progenitors and angiogenic factors could promote cardio-circulatory rehabilitation and accelerate cardiogenesis. This approach might eliminate the need for interventional or surgical procedures.

Finally, as far as the concept has been proven therapeutic efficiencies, there were some study limits that should be resolved in the future. This includes the severe vasodilatation as a result of direct intravascular endothelial stimulations by the intrapulmonary pulsatile catheter as well as the pulsatile tube as a LVAD.

Interestingly, the application of the pulsatile tube alone as a LVAD without perfusion pump induced severe vasodilatation after impressive improvement of MI (please refer to operative movie). This is proving the hypersensitivity of the pulmonary endothelium as well as the LV endocardium that were responded rapidly to the unsynchronized tube pulsations.

A similar phenomenon has been observed with Nicorandil, an exogenous NO donor used for angina pectoris relief (Falase BA, et al., 1999), (Blanc P, et al., 2001).

Meanwhile, vasodilatation that could be induced by exogenous NO donors, leads to hypovolemic-cardiogenic shock. In contrast, the observed study hypovolemia, was preceded by general improvement of hemodynamic and organ microcirculation. This was manifested by the increased renal output manifested by a vesical globe that was released spontaneously in the pulsatile group animal models, which could be easily compensated by IV fluids. Currently we reduced the frequencies of pulsatile time (5-10 min), interrupted by interval pause guided by hemodynamic monitors, particularly systemic BP.

There was no observed severe vasodilatation with the externally stimulated endothelial devices (the pulsatile trouser and mask). By caution, as the mechanism of vasodilatation is still undiscovered, also the improved microcirculation became almost steady after 15-20 min of external endothelial stimulations, our recommendation for the pulsatile suit sessions is: 20-30 min. Furthermore, it is unnecessary to apply high-pressure pulsatile volume. A low pressure (1.2-2 bars) is sufficient to stimulate the superficial intravascular blood volume, covered by their endothelial stocks.

Contraindications of the pulsatile suit, are more or less relatives as a non-invasive device, meanwhile cautions may be considered with some patients (e.g. hepatic cirrhosis, malignancy, open fractures, 3rd degree burns, colostomy, cerebral accidents, malignancy). Under all circumstances, Clinicians will determine contraindications according to the obtained results.

Currently, clinical programs of the non-invasive devices will start very soon, with (Type A, & C) endothelial dysfunction patients (e.g. CHF, resistant arterial hypertension, cerebral atherosclerosis, etc.) and others with healthy persons (Type C) e.g. bedridden, athletes.

12. Conclusion

A promising therapeutic approach for CVD and circulatory disorders management with more physiological cost effective manners compared to current therapies. According to physics, it consists of: a shear rate intravascular enhancement device (catheter); a steady flow transformer device (tube) and an accessory circulatory driving forces enhancement and/or replacement device (suit). Drawbacks of the invasive devices could be overruled through accurate mathematical calculations of the induced momentum according to individual body surface area and the stimulated sites (blood column). Means, optimum devices performances could be achieved with computational models and biomedical engineering, to define the accurate device geometries as well as materials.

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Pascal, Blaise (1623-1662)

**“The all our advantage is in our ability to think.
Only idea uplifts us instead of space and time,...The only our thinking is a basis of morals”**

Thank You

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RESUME

Le cœur et les vaisseaux sanguins sont directement issus de l'endothélium et dépendent de sa fonction. Le cœur ne représente pas la seule force motrice de notre système circulatoire. Cette thèse est basée sur l'activation de la fonction endothéliale. Ce concept permet une meilleure gestion thérapeutique des maladies circulatoires et cardio-pulmonaires.

MOTS-CLES

Défaillance circulatoire et cardio-pulmonaires. Force de cisaillement. Fonction endothéliale. Assistance circulatoire pulsatile.

Laboratoire de Recherches Biochirurgicales, Université Paris Descartes. Hôpital Européen Georges Pompidou, Fondation Alain Carpentier.

POLE : PHYSIOPATHOLOGIE MOLECULAIRE ET CELLULAIRE

UNIVERSITE PARIS-SUD 11

UFR « FACULTE DE PHARMACIE DE CHATENAY-MALABRY »

5, rue Jean Baptiste Clément

92296 CHATENAY-MALABRY Cedex